POTENTIAL TRANSMISSION OF SPONGIFORM ENCEPHALOPATHIES TO HUMANS: THE FOOD AND DRUG ADMINISTRATION'S [FDA] RUMINANT TO RUMINANT FEED BAN AND THE SAFETY OF OTHER PRODUCTS

HEARING

BEFORE THE

COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT HOUSE OF REPRESENTATIVES

ONE HUNDRED FIFTH CONGRESS

FIRST SESSION

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POTENTIAL TRANSMISSION OF SPONGIFORM ENCEPHALOPATHIES TO HUMANS: THE FOOD AND DRUG ADMINISTRATION'S [FDA] RUMINANT TO RUMINANT FEED BAN AND THE SAFETY OF OTHER PRODUCTS

WEDNESDAY, JANUARY 29, 1997

HOUSE OF REPRESENTATIVES,
COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT,
Washington, D.C.

The committee met, pursuant to notice, at 1:10 p.m., in room 2247, Rayburn House Office Building, Hon. Christopher Shays (chairman of the Subcommittee on Human Resources) presiding.

Present: Representatives Shays, Pappas, Waxman, and Towns.

Staff present: Lawrence J. Halloran, staff director and counsel; Anne Marie Finley and Robert Newman, professional staff members; R. Jared Carpenter, clerk; Phil Barnett, minority chief counsel; Agnieszka Fryszman, minority counsel; and Ellen Rayner, minority chief clerk.

Mr. SHAYS. I would like to call this hearing to order and acknowledge that this is the Human Resources Subcommittee of the Government Reform and Oversight Committee, but given that the committee has not officially established its subcommittees, we are operating at the permission of the chairman and ranking member, who have authorized this committee to proceed.

I would like to welcome our witnesses and our guests. I have a statement, as does Mr. Towns, and Mr. Waxman has a statement as well.

In the last Congress, this subcommittee devoted considerable time to an examination of the Federal approach to emerging infectious agents, particularly foodborne pathogens. The central question then, and now, is: What is the appropriate regulatory response to a public health threat about which there is little conclusive scientific information, small known risk, but theoretical risks of serious, even calamitous, spread of infection?

Transmissible spongiform encephalopathies, TSEs, constitute a class of degenerative, fatal diseases that attack the brain. TSEs infect numerous mammal species including sheep, cows, deer, elk, goats, minks, and humans. The causative agent is not known. There is no diagnostic test to detect the presence of a TSE, only a postmortem dissection.

The TSE in sheep, called scrapie, has been known for more than 200 years, with the disease posing no known threat to human health or the safety of the human food supply. TSEs emerged as

a public health issue only in the late 1980's when an epidemic of bovine spongiform encephalopathy, BSE, or "mad cow disease," struck British dairy and beef cattle.

The source of that outbreak is not known, but it is believed the incidence and virulence of the disease were amplified by what is called ruminant-to-ruminant feeding—the use of ruminant animals, sheep, cows and goats, in feeds for ruminant animals. In Great Britain, sick cows and sheep were ground into feed for healthy cows, which then became infected.

In tragic proof of the adage "you are what you eat," it now appears that consumption of BSE-infected beef was responsible for the emergence in Britain of a variant form of the human TSE, Creutzfeldt-Jakob disease.

While no BSE has been reported in the United States, the U.S. Department of Agriculture, USDA, and the public health agencies of the Department of Health and Human Services, HHS, have taken steps to prevent its emergence here. In 1989, USDA banned the importation of meat and other potentially infected products from countries in which BSE exists.

Last year, the FDA testified before this subcommittee that regulatory action was imminent on a ruminant-to-ruminant feed ban as a preemptive safeguard against the appearance or the amplification of TSEs in meat animals entering the U.S. food supply.

Today, 8 months later, we will discuss the timing and substance of the FDA proposal to prohibit certain ruminant-to-ruminant feeding practices. In the weeks ahead, we will hear from producers and consumers about other steps that might afford additional public health protections against TSEs.

Other steps may be necessary because the food chain is not the only possible vector for TSEs to emerge as a public health problem. There is a theoretical danger that CJD can be transmitted through blood and blood products. There is some concern the suspected infective agent, the prion, survives the processing of cow remnants into the oils and gelatins used in making cosmetics, drug capsules, and a variety of other products.

Therefore, we ask: How should these risks be evaluated in the absence of definitive scientific evidence? What practical and proactive public health policies will minimize those risks? What research will clarify the causes, courses and cures of TSE diseases?

We learned the hard way with hepatitis and AIDS that emerging infectious agents can slip past our public health defenses unless we vigilantly maintain an early warning system sensitive to probability as well as proof. Better to protect against unproven risks than wait for proof that may only emerge in increased mortality statistics.

Some say "mad cow disease" is a misnomer because the afflicted animals appear more worried than mad. They are not the only ones, frankly, that are worried, but our worry should not be misconstrued. Valid public health concerns should not be sensationalized into unsubstantiated fears about the U.S. food supply, which is, without question, among the safest in the world.

Our goal is the proactive protection of the public health, and in that regard we welcome our witnesses today in that effort. And in this, I would now like to call on Mr. Towns, who has been, frankly, while I am chairman, he is ranking member, and a copartner in this committee and the good work we are doing.

[The prepared statement of Hon. Christopher Shays and the information referred to follow:]

ONE HUNDRED FIFTH CONGRESS

Congress of the United States

House of Representatives

COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT

2157 Rayburn House Office Building

Washington, DC 20515–6143

SUBCOMMITTEE ON HUMAN RESOURCES

Christopher Shays, Connecticut
Chairman
Room B-372 Rayburn Building
Washington, D.C. 20515
Tel: 202 225-2548
Fax: 202 225-2382

Statement of Rep. Christopher Shays
January 29, 1997

In the last Congress, this Subcommittee devoted considerable time to an examination of the federal approach to emerging infectious agents, particularly food borne pathogens. The central question then, and now: What is the appropriate regulatory response to a public health threat about which there is little conclusive scientific information, small known risk but theoretical risks of serious, even calamitous, spread of infection?

Transmissible spongiform encephalopathies (TSEs) constitute a class of degenerative, fatal diseases that attack the brain. TSEs infect numerous mammal species including sheep, cows, deer, elk, goats, minks and humans. The causative agent is not known. There is no diagnostic test to detect the presence of a TSE. Only a *post mortem* dissection of the brain confirms the disease.

The TSE in sheep, called scrapie, has been known for more than two hundred years, with the disease posing no known threat to human health or to the safety of the human food supply. TSEs emerged as a public health issue only in the late 1980s when an epidemic of bovine spongiform encephalopathy (BSE), or "Mad Cow Disease," struck British dairy and beef cattle.

The source of that outbreak is not known, but it is believed the incidence and virulence of the disease were amplified by what is called "ruminant to ruminant feeding" - the use of ruminant animals (sheep, cows and goats) in feeds for ruminant animals. In Great Britain, sick cows and sheep were ground into feed for healthy cows, which then became infected.

In tragic proof of the adage "You are what you eat," it now appears consumption of BSE-infected beef was responsible for the emergence in Britain of a variant form of the human TSE, Creutzfelt-Jakob Disease (CJD).

While no BSE has been reported in the United States, the U.S. Department of Agriculture (USDA) and the public health agencies of the Department of Health and Human Services (HHS) have taken steps to prevent its emergence here. In 1989, USDA banned the importation of meat and other potentially infected products from countries where BSE exists.

In May of last year, the Food and Drug Administration (FDA) testified before this Subcommittee that regulatory action was imminent on a ruminant-to-ruminant feed ban as a preemptive safeguard against the appearance or amplification of TSEs in meat animals entering the U.S. food supply.

Today, eight months later, we will discuss the timing and substance of the FDA proposal to prohibit certain ruminant to ruminant feeding practices.

In the weeks ahead, we will hear from producers and consumers about other steps that might afford additional public health protections against TSEs.

Other steps may be necessary because the food chain is not the only possible vector for TSEs to emerge as a public health problem. There is a theoretical risk that CJD can be transmitted through blood, and blood products. There is some concern the suspected infective agent, the prion, survives the processing of cow remnants into the oils and gelatins used in making cosmetics, drug capsules, and a variety of other products.

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Our goal is the pro-active protection of the public health, and we welcome all our witnesses today in that effort.

ONE HUNDRED FIFTH CONGRESS

Congress of the United States

House of Representatives

COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT

2157 RAYBURN HOUSE OFFICE BUILDING

WASHINGTON, DC 20515–6143

January 16, 1997

The Hon. Christopher Shays
1502 Longworth Building
Washington, D.C. 20515

Dear Chris:

Pursuant to my agreement with the Ranking Member, you are authorized to conduct two hearings prior to the adoption of Committee Rules. Specific topics for the hearings are set out in my January 7 letter to Rep. Waxman memorializing our agreement. (copy attached)

I understand you will convene the first hearing on January 21 on Persian Gulf War veterans' illnesses, with the second hearing, on the Food and Drug Administration's safety standards regarding transmissible spongiform encephalopathies, to be held on January 29.

Pursuant to the Rule XI, clause 2(m)(1) of the Rules of the House, you are hereby designated to administer oaths to witnesses at the hearings.

In the absence of Committee Rules, it is understood the hearings will be conducted in accordance with the Rules of the House, and to the extent practicable, under the Committee Rules adopted for the 104th Congress.

Sincerely,

Dan Burton
Chairman

cc: Rep. Henry Waxman
Rep. Chris Cox

Mr. TOWNS. Thank you. I would like to yield to the ranking member of the committee to go first.

Mr. WAXMAN. You want me to go first?

Mr. SHAYS. I would be happy——

Mr. TOWNS. It is different protocol. You are going to have to organize the committee.

Mr. SHAYS. Let me keep protocol and call on Mr. Waxman to yield to Mr. Towns.

Mr. WAXMAN. Mr. Towns is the ranking member of the subcommittee from last year but hasn't officially been made ranking member this year. I have full expectation that he will be, and I would like to yield to him.

Mr. TOWNS. Thank you very much.

First, let me thank you, Mr. Chairman, for calling this hearing this afternoon. We will hear from the agencies charged with protecting the health and safety of the American public, and from members of the scientific community; I also believe we need to hear from consumer groups and representatives of the industry that will be impacted by what decisions we make here. I am glad the chairman plans to have another hearing on this topic so that all voices can be heard and so we can ensure we are all working cooperatively to make certain that our food supply is safe.

BSE has had a devastating impact in Great Britain where hundreds of thousands of cattle have been destroyed to prevent the spread of the disease. We are fortunate that no cases of BSE have been reported in the United States.

Since 1989, the U.S. Department of Agriculture has banned the importation of live ruminants of cattle, sheep, and goats, and ruminant products from countries where BSE exists. British beef has not been imported to the United States since 1985. The FDA is now taking an additional step, banning the use of ruminants, tissues, and ruminant feed, which will cutoff the primary means of transmission of BSE.

The jury is still out on what causes BSE and whether BSE in cattle is transmissible to humans. Research in this area is ongoing. But let me add, I agree with the chairman that more research is necessary and we should move aggressively to make certain that we get information. Given the lack of concrete scientific data that is currently available, I am interested in hearing from the witnesses as to what, if any, additional steps are necessary at this time.

Thank you again, Mr. Chairman, and I look forward to hearing from the witnesses and working with you to make certain that our food supply continues to be safe. Thank you.

Mr. SHAYS. Thank you, Mr. Towns.

Before calling on Mr. Waxman, I will invite Michael Pappas, who is a new member of this committee and a welcomed addition.

Mr. PAPPAS. Thank you, Mr. Chairman.

I would like to thank you and the members of this committee and these witnesses and all of those interested for taking time to share their concerns with us today and in any subsequent hearings. The world's greatest enemies seem to be getting stronger, yet tinier and harder to control, every year. These tiny dangers in the form of bacteria, viruses, parasites, and prions continue to chal-

lenge our scientific knowledge and force the scientists to work harder each year.

Hollywood fears of a great disease wiping out humans and/or animals are only exacerbated by the real-life horrors in the news of the Ebola virus and now "mad cow disease." As a public official, I believe it is my duty to assist in placating any fears of the public and the agricultural community by ensuring that adequate steps are in place to assure the continued safety of our citizens and our unparalleled agricultural industry. However, it is my duty to ensure that the cure fits the problem, and that government does not overreact to a problem that may not exist, or impose a cure that could be considered, for lack of a better term, overkill or recklessly trample over the rights of individuals in government's desire to do right. In such, I am hopeful we will maintain a balanced, reasoned approach to this serious issue and propose rules based on facts, not fears.

Finally, I would like to welcome Dr. Linda Detwiler, who is based in New Jersey, as a witness before this panel. When I talk about agriculture in New Jersey, it is good to know that the witness will have had firsthand experience with it, and I look forward to hearing from her and other witnesses.

Thank you, Mr. Chairman.

Mr. SHAYS. Thank you, Mr. Pappas.

Mr. Waxman, who I might point out is the ranking member of the full committee and also was chairman on the Commerce Committee, the subcommittee that dealt with all environmental and health issues, so it is wonderful to have you here today.

Mr. WAXMAN. Thank you, Mr. Chairman, and I am pleased that you have called this hearing.

This country has the safest food supply in the world and we want to keep it that way. We also want to ensure that American consumers do not lose confidence in the safety of the products that they and their children use every day, so I am glad we are here to determine whether more needs to be done to protect against the possible transmission of BSE. In particular, I want to commend you, Mr. Chairman, for your leadership in this area. Your continued interest has been essential in prompting FDA regulation.

But I must say that I find it very ironic that in this committee we are talking about what the FDA needs to be doing while down the hall other committees are trying to reduce the authority of the Food and Drug Administration.

We will continue to face threats to our food supply, threats that we know about and threats that are real. We have enough scientific information to know that they are serious threats, like the E. coli outbreak we suffered last year, and potential threats to our blood supply through new and emerging diseases. That is why we need a strong and effective FDA as well as a strong and effective line of defense at USDA and the Centers for Disease Control and Prevention.

In the last Congress, many Republican Members, and some Democrats, were pressing for a reduction in the FDA's regulatory abilities and a weakening of the agency's ability to enforce the law. Some in Congress, also tried to legislate away the ability of agen-

cies to make sound, science-based decisions in a reasonable period of time.

I am particularly concerned about how Congress has restricted the FDA's authority to regulate dietary supplements. We recently enacted the Dietary Supplement Health and Education Act under a great deal of pressure from the industry. Some of these dietary supplements are produced from animal tissues. Now, we don't know if that is a reason to be concerned, but under the provisions of this new law, the manufacturer of these products is subject to very little regulatory oversight. In fact, Congress went so far as to block FDA from acting until FDA can prove the dietary supplements are harming people. As a result, FDA can do very little to reduce any BSE threat in these products, should one develop.

I think the point has been made by the other members of this panel. We don't want to scare people into thinking that there is a crisis. We don't want to overreact. We want to act in a balanced, reasonable manner. We have agencies like the FDA, the USDA, and the Centers for Disease Control, to give us that appropriate balance. But as they design the appropriate balance, we have got to give them the regulatory tools to act when it is necessary and not hamper them from acting when it is in their best judgment, based on the facts and the science, that there is a reason to act.

So I am pleased we are holding this hearing, Mr. Chairman, and I want to commend you for your leadership. This is an important issue and deserves an airing in the Congress.

Mr. SHAYS. I thank the gentleman.

[The prepared statement of Hon. Henry A. Waxman follows:]

Statement of Rep. Henry A. Waxman
January 29, 1997

Mr. Chairman, thank you for holding this hearing today. This country has the safest food supply in the world. And we all want to keep it that way. We also want to ensure that American consumers do not lose confidence in the safety of the products that they and their children use every day.

I am pleased that we are here to determine whether more needs to be done to protect against the possible transmission of bovine spongiform encephaly (BSE). In particular, I want to commend the Chairman for his leadership in this area. His continued interest has been essential in prompting FDA regulation.

But I must say that I find it very ironic that in this Committee we are talking about what the FDA needs to be doing while just down the hall, other committees are trying to reduce the authority of the FDA.

We will continue to face threats to our food supply -- like the e-coli outbreak we suffered last year -- and potential threats to our blood supply through new and emerging diseases. That is why we need a strong and effective FDA as well as a strong and effective line of defense at USDA and CDC.

In the last Congress, many Republican Members were pressing for a reduction in FDA's regulatory abilities, and a weakening of the agency's ability to enforce the law. Congress also tried to legislate away the ability of agencies to make sound science-based decisions in a reasonable period of time.

I am particularly concerned about how Congress has restricted the FDA's authority to regulate dietary supplements. We recently enacted the Dietary Supplement Health and Education Act under a great deal of pressure from industry. Some of these dietary supplements are produced from animal tissues. Under the provisions of this new law, the manufacture of these products is subject to very little regulatory oversight. In fact, Congress went so far as to block FDA from acting until FDA can prove that dietary supplements are harming people. As a result, FDA can do very little to reduce any BSE threat in these products -- should one develop.

I look forward to today's testimony.

Mr. SHAYS. Let me just get some housekeeping out of the way: I ask unanimous consent that all members of the subcommittee be permitted to place any opening statements in the record and that the record remain open for 3 days for that purpose, and without objection, so ordered.

Also, I would ask unanimous consent that witnesses be permitted to include written statements in the record if they choose to summarize them. Without objection, so ordered.

At this time, as is the practice, we will swear in all our witnesses, including Members of Congress, and I would invite you to rise and raise your right hand. I am assuming, since I see others standing up and raising their right hand, that you are backup staff. If they say something for the record, they will have to be sworn in.

[Witnesses sworn.]

Mr. SHAYS. For the record, our main witnesses have answered in the affirmative and as well as others who have accompanied them.

I would like to apologize to the people in the audience. Next time we will have the witness table up closer and have a few more rows of chairs. It may be some won't stay too long and seats will become available.

At this time, let me just recognize our witnesses. We have Michael Friedman, who is the Deputy Commissioner for the Food and Drug Administration, FDA. He will kind of give us the human health care element here. We have Linda Detwiler, chairman of the TSE working group from the U.S. Department of Agriculture. She will give us the animal health perspective. We have, as well, Lawrence Schonberger, who is the assistant director for Public Health, National Center for Infectious Diseases, Centers for Disease Control and Prevention, CDC, and he will give us a sense of disease detection. Then we have Clarence J. Gibbs, acting chief, National Institutes of Neurological Disorders and Stroke, National Institutes of Health, for the focus on research into this disease.

Let me just say, all of you are doctors, so I didn't introduce you as doctors. You are all experts and we are eager to hear your testimony and welcome you. And if we could go in the order I called you, that would be helpful. Dr. Friedman.

STATEMENTS OF MICHAEL FRIEDMAN, M.D., DEPUTY COMMISSIONER, FOOD AND DRUG ADMINISTRATION; LINDA DETWILER, D.V.M., U.S. DEPARTMENT OF AGRICULTURE, ANIMAL AND PLANT HEALTH INSPECTION SERVICE, ACCOMPANIED BY GLENN MORRIS, FOOD SAFETY INSPECTION SERVICE, USDA; LAWRENCE SCHONBERGER, M.D., CENTERS FOR DISEASE CONTROL AND PREVENTION; AND CLARENCE J. GIBBS, JR., PH.D., NATIONAL INSTITUTES OF HEALTH

Dr. FRIEDMAN. Thank you very much, Mr. Chairman, and members of the committee. We appreciate this opportunity to participate in today's discussions on measures to prevent the transmission of spongiform encephalopathies. I am Michael Friedman, and I am the Deputy Commissioner for Operations in the Food and Drug Administration, and with me are a number of relevant staff to aid you in your considerations.

TSEs, as you know, are transmissible, slowly progressive, uniformly fatal, degenerative diseases of the central nervous system, not only of humans but several species of animals as well. Examples of TSEs that we will be discussing today include scrapie in sheep and goats, bovine spongiform encephalopathy, or BSE, in cattle, transmissible mink encephalopathy, and a chronic wasting disease of deer and elk in the wild.

In humans, there are a number of TSEs, but of note today especially is Creutzfeldt-Jakob disease, which will be referred to as CJD for short.

Mr. SHAYS. Thank goodness.

Dr. FRIEDMAN. A rare disease, CJD effects roughly one to two persons per million each year worldwide. This rate appears not to have been increasing despite much more intensified monitoring of the disease since the mid-1980's.

As you pointed out, Mr. Chairman, a major concern for this committee has been BSE, and I'd like to reiterate the point that was made earlier, this disease which was so destructive in Great Britain has not been detected in this country, and since 1989, no cattle have been imported from BSE countries as designated by USDA.

Now, in recent years, FDA has made an effort to better understand and prevent the possible spread of TSEs. We have acted alone but also in concert with the Centers for Disease Control, the National Institutes of Health, and the U.S. Department of Agriculture, as well as relevant industries and consumer groups. The seating arrangement at this table is symbolic of that real cooperation and collaboration in this regard. Our activities and our formal internal and external linkages in this framework are described much more fully in my written statement.

I would like to briefly summarize two major efforts that we've undertaken and your committee has expressed specific interest in. The most recent major measure is FDA's proposed rulemaking to prohibit the use of nearly all tissues from ruminants, animals such as cows and sheep and goats, and from mink as well, in feed intended for other ruminants. However, earlier, since November 1992, FDA has been asking manufacturers of regulated products to ensure that they do not use materials from countries where BSE-infected cattle may reside.

Our first warning in this regard was sent to manufacturers of dietary supplements, but we eventually sent similar requests to all industries in our purview that use animal tissues or animal-derived materials. FDA-regulated products that could contain bovine tissues are many, but include animal feed, human and animal drugs and biologics, dietary supplements, medical devices, and cosmetics.

The recent reports of a possible linkage between BSE and a new variant of CJD and humans has prompted us to take a more comprehensive look at and to take more comprehensive steps to assure the safety of ruminant feed, which as you noted earlier, seems to have been the main source of the infection in the United Kingdom.

Our notice of proposed rulemaking in this regard, which is supported by last year's recommendation from the World Health Organization and other agencies and industry groups, will help assure that animal protein derived from ruminant and mink tissues is not

marketed as a food additive in ruminant feed until FDA is presented with scientific data demonstrating it to be safe. Such data do not exist at this time.

This precaution is based on evidence that TSE-infected sheep and cattle tissue in cattle feed seems to have caused and to have amplified the BSE epidemic in the U.K. We are currently seeking public comments on our proposal as well as six alternative measures that we also have stated in our proposal, and which are summarized in my written statement, and we plan to discuss these measures with interested parties at two public fora over the next month. We believe that the proposed step would be significant help in preventing the spread of disease in the unlikely event the disease should occur in this country, and we regard the concerns as fully justifying this proposal.

Another major set of actions that we've taken in this area is to address the otherwise CJD bloodborne transmission and reduce such risk, if it exists at all. Our blood supply is amongst the safest in the world, and we know of no reported instances of CJD transmission through blood. In fact, scientists have been unable to transmit CJD to subhuman primates by infusing them with blood from a CJD patient. The scientists think the data are not complete in this area.

There are some studies that suggest that there may be reason for concern, but while there is much we do not know about CJD, we recognize the disease has a long incubation period during which it is currently undetectable, and there is no serum test available for us to detect it.

Aware of these problems and limitations, FDA has been working very closely with CDC and NIH as well as blood and plasma recipients, medical professionals, academicians, and blood product industry scientists to determine the most appropriate protective actions to be taken. Nine years ago, our agency issued a memorandum to all blood establishments recommending that persons who had received human pituitary-derived growth hormone, a substance which has been linked to the development of CJD in human beings, be barred from donating blood.

Three years ago, FDA issued recommendations for more complete reporting by blood establishments of post-donation information. This improved identification of blood products in donors subsequently diagnosed with CJD.

In 1994, at FDA's request, the manufacturers placed the identified end-date licensed injectable derivatives of blood and plasma, and their intermediates, into quarantine, and in June 1995, the agency discussed their disposition at a meeting of our special advisory committee on CJD. Acting on the advice of that panel, FDA in August 1995 issued an interim policy that called for blood products from donors later diagnosed with CJD to be discarded.

Since then, FDA has consulted extensively with experts in this field, and last month we revised and refined our policy further in making the following recommendations in order to best utilize medically valuable products while still protecting the public health. In particular, we emphasized the importance of donor deferral, the need for a careful investigation of a family history of CJD, which

could be then confirmed by a physician on the basis of diagnostic and history taking procedures currently available.

Mr. Chairman, we are making every effort to improve the safety of our food and our blood supply. We will continue to evaluate new information, recognizing how much we yet do not know about practical aspects of the TSEs, and consider adopting appropriate public health actions and policies. We do so collaboratively from both within and outside of government, and I look forward to an opportunity to answer questions that may arise. With me are staff who will help in that regard.

Thank you for this opportunity.

Mr. SHAYS. Thank you, Dr. Friedman.

[The prepared statement of Dr. Friedman follows:]

STATEMENT BY

MICHAEL A. FRIEDMAN, M.D.

DEPUTY COMMISSIONER FOR OPERATIONS

FOOD AND DRUG ADMINISTRATION

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT

SUBCOMMITTEE ON HUMAN RESOURCES AND

INTERGOVERNMENTAL RELATIONS

U.S. HOUSE OF REPRESENTATIVES

JANUARY 29, 1997

FOR RELEASE ONLY UPON DELIVERY

Mr. Chairman, Members of the Committee, thank you for the opportunity to participate in today's hearing on the proposed rule on the ruminant to ruminant feed ban and the potential transmission of spongiform encephalopathies to humans. My name is Dr. Michael Friedman and I am the Deputy Commissioner for Operations at the Food and Drug Administration (FDA).

FDA is the nation's oldest consumer protection agency, responsible for the safety and effectiveness of over $1 trillion worth of products and commodities. We have been protecting consumers against an ever-growing number of public health risks for over nine decades, and we have not done it by standing still. FDA constantly is being presented with new questions, for which we are committed to seeking and finding answers, while applying current statutes, state of the art science, and knowledge gained from our experiences in responding to previous public health risks.

FDA's responsibilities encompass drugs for use in people and animals, human biological products, medical devices, food, dietary supplements, cosmetics, and animal feeds. Each of these product groups has been considered with respect to the potential for the transmissible spongiform encephalopathies (TSEs) in humans or animals. As you may know, TSEs are a group of transmissible, slowly progressive, degenerative diseases of the

central nervous systems of humans and several species of animals. This family of diseases is characterized by a long incubation period, a relatively short clinical course of neurological signs, and 100 percent mortality. Examples of TSEs are scrapie in sheep and goats, bovine spongiform encephalopathy in cattle, transmissible mink encephalopathy, chronic wasting disease of deer and elk, and Creutzfeldt-Jakob Disease (CJD) and kuru in humans.

FDA has been involved actively in national and international efforts focused on better understanding TSEs. FDA has collaborated extensively with its sister Public Health Service Agencies, the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH), and with the United States Department of Agriculture (USDA), as well as with affected industries and consumer groups. FDA has formed an intra-agency working group composed of myself and experts from each FDA Center to consider transmissible spongiform encephalopathies and their impact on FDA-regulated products. A CJD Advisory Committee, composed of outside experts, including academic and government representatives; consumer groups, including the National Hemophiliac Foundation; and industry groups, also was formed in 1995, and was rechartered in June 1996 for two additional years as the TSE Advisory Committee.

I. BOVINE SPONGIFORM ENCEPHALOPATHY (BSE)

Bovine spongiform encephalopathy (BSE), also referred to as "mad cow disease," is thought to be a transmissible, slowly progressive, degenerative disease of the central nervous system of cattle, and is similar to scrapie in sheep. BSE has a prolonged incubation period in cattle (three to eight years) following oral exposure and, as with all TSEs, once symptoms appear, BSE invariably is fatal. There is no known treatment or cure. That said, we emphasize that BSE has not been detected in cattle in the U.S., and since 1989, no cattle have been imported from BSE countries as designated by the USDA.

Since BSE was first diagnosed in the United Kingdom (UK) in November 1986, more than 165,000 cattle from almost 33,000 herds have been diagnosed with the disease. BSE now has been reported in native cattle in France, Switzerland, Portugal, the Republic of Ireland, and Northern Ireland. The epidemic in the UK peaked in January 1993 at nearly 1,000 new cases per week; currently fewer than 200 suspected cases are diagnosed every week. The disease has had a devastating impact on the cattle and beef industry in the UK where hundreds of thousands of suspect cattle have been killed and incinerated to prevent further spread of the disease.

Epidemiological studies, including computer simulation of the epidemic in the UK, suggest that feeding cattle rendered meat and bone meal from animals infected with some TSE agent was the vehicle for the spread of the disease. The practice of adding meat and bone meal to animal feed has become a common way for producers to supplement their animals' protein and other dietary needs. Possible hypotheses as to the original UK source of the TSE agent are: 1) that it was a modified form of scrapie transmitted via rendered by-products of sheep, or 2) that it was a cattle-adapted strain of a scrapie-like agent, also spread via feed. Both theories are consistent with the epidemiological findings. Of particular importance, recent research in the UK suggests that the BSE agent is resistant to the rendering processes used in that country. This research further supports the epidemiological evidence that the disease has been spread through rendered meat and bone meal added to cattle feed. Scientists also have theorized, however, that BSE could occur spontaneously in cattle, though presumably at a very low rate.

Possible Link Between BSE and CJD

Scientists also have theorized about the impact of BSE on human health and its possible link to CJD. CJD is a slow degenerative human disease of the central nervous system characterized by motor dysfunction, progressive dementia, and vacuolar

degeneration of the brain. The incidence of CJD in the U.S. is similar to the incidence in the rest of the world. Sporadic cases of CJD occur world-wide at a rate of one case per million population per year.

On March 20, 1996, the British Government announced a possible link between BSE and ten cases of a new type of CJD in humans. These recent cases appear to represent a new variant of CJD (nv-CJD) that seems to be unique. At a World Health Organization (WHO) consultation in April 1996, a group of international experts concluded that there is no definite link between BSE and this small group of people with nv-CJD, but epidemiological evidence suggests exposure to BSE before the UK specified tissue ban in 1989 may be the most likely explanation. To date, scientists have identified the distinctive nv-CJD brain pathology in 15 people with CJD in BSE countries (14 in the UK, 1 in France). In October 1996, Dr. John Collinge, one of the foremost British authorities on CJD, and his colleagues published the results of their research on various strains of the agents believed to transmit BSE. The results suggest that the agent found in nv-CJD resembles the BSE agent rather than the sporadic CJD agent.

As stated, BSE has not been detected in cattle in the U.S., and since 1989, no cattle have been imported from BSE countries as

designated by USDA. Nevertheless, the possible link between nv-CJD and BSE, and new information about the origin and etiology of the BSE agent have prompted the public, the U.S. Government and affected industries to view this disease very seriously. As a result, several important measures have been undertaken to further reduce the remote risk of BSE occurring in the U.S. It should be stressed, however, that there is no established scientific link between BSE and CJD in humans.

Proposed Rule: Ruminant and Mink to Ruminant Feed Ban

One critical measure is the issuance by FDA of a Notice of Proposed Rule Making (NPRM) to prohibit the use of nearly all tissues from ruminants -- animals such as cows, sheep, and goats -- in feed intended for ruminants. Mink tissue also would be prohibited from such feeds, because of known cases of TSE in mink raised in the U.S. The prohibition on feed ingredients proposed in the NPRM is intended to prevent the spread of BSE in cattle in the unlikely event that the disease should ever occur in this country, and to further minimize any risk that might be posed to humans. The NPRM was published in the Federal Register on January 3, 1997, after FDA completed an in-depth review of the 660 comments it received last year in response to its advance notice of proposed rulemaking related to the feed ban. These comments covered many of the scientific and economic issues

addressed in the NPRM. FDA's proposal to ban the use ruminant and mink proteins in ruminant feed follows a voluntary industry moratorium on similar feeding practices instituted in March 1996 by national livestock organizations and professional animal health groups and endorsed by FDA, CDC, NIH, and the USDA. The finalization of the proposal will add another level of safeguards to protect the U.S. against the remote potential risk from TSEs. Moreover, FDA's proposed regulation is supported by last year's WHO recommendations for countries in which no BSE has been diagnosed.

The NPRM provides that animal protein derived from ruminant and mink tissues are not generally recognized as safe (GRAS) for use in ruminant feed and is a food additive subject to section 409 of the Federal Food, Drug, and Cosmetic (FDC) Act. The determination of food additive status for this substance (protein derived from ruminant and mink tissues) will help to ensure that it will not be marketed in the U.S. until such time as FDA determines it to be safe. The NPRM proposes to exempt from the ruminant protein feed ban three tissue types that have shown no signs of potential infectivity. These exceptions include bovine blood, ruminant-derived milk, and gelatin. A second component of the rule provides for a system of processes and controls, including record keeping and labeling, that is necessary to ensure the proposed rule will achieve its intended purpose.

Based on the overwhelming evidence we have on transmissibility, if for some reason a case of BSE were to occur in the U.S., and it is important to reemphasize that not even one case of BSE has ever been found here, the steps being proposed in the NPRM would confine it to the individual animal and greatly decrease the potential risk to other animals and humans.

The preamble to FDA's proposed rule points out that FDA is considering alternatives to the proposed ruminant and mink protein to ruminant prohibition and that it also is seeking comments on those alternatives, which include a(n): (1) Adult sheep and goat specified offal to ruminant prohibition; (2) Prohibition to ruminants of all materials from U.S. species which have been diagnosed with TSEs (sheep, goats, mink, deer, and elk); (3) Partial ruminant to ruminant prohibition; (4) Mammal to ruminant prohibition; (5) No regulatory action; and, (6) Other alternative approaches that meet FDA's regulatory objective.

Although BSE does not exist in the U.S., we believe that the preventive approach FDA is taking in the NPRM is justified by what we now know about this disease and how it is caused and spread. As noted above, epidemiological evidence corroborates the theories that the origin of BSE was caused by the feeding to cattle of meat and bone meal either containing the scrapie agent

from rendered by-products of sheep, or a cattle-adapted strain of a scrapie-like agent from rendered by-products of cattle. Current U.S. rendering techniques would decrease, but probably not totally eliminate the BSE agent. Since sheep scrapie and other animal-borne TSEs already are known to exist in the U.S., the epidemiological evidence indicates that BSE could possibly develop and be spread here under unrestricted feeding practices. Moreover, the risk that BSE-infected cattle or feed could be imported inadvertently from BSE infected countries, or that BSE could occur spontaneously further supports the preventive strategy proposed in the NPRM. The strategy provided in the NPRM also is supported by the steady decline in the number of cases of BSE in the UK after they established similar restrictions on ruminant feeding practices.

Comments are being solicited by FDA on all aspects of the NPRM, including the scope of the ban and the list of exempted tissue types. A 45 day public comment period expires on February 18, 1997. To facilitate notice and comment on the NPRM, in addition to providing the proposed rule to the CDC, NIH and the USDA, FDA provided a copy of the proposed rule to the group of international experts interested in BSE. The document was delivered to heads of foreign public and animal health organizations and to appropriate officials of our major animal products trading countries. During February, FDA will hold two

open public forums to discuss the notice of proposed rule making to prohibit the use of rendered ruminant and mink protein products in ruminant feeds. Comments may be submitted to the Dockets Management Branch, Food and Drug Administration, 12320 Parklawn Drive, Room 1-23, Rockville MD 20857. These comments will be reviewed by the Food and Drug Administration and will be used in preparing final regulations.

FDA recognizes that American consumers look to us to assure the safety of the U.S. food supply. We believe that the strong preventive strategy provided in the NPRM is supported by the best available science on BSE and that this approach significantly reduces risk to animal health and any perceived risk to human health. As the scientific knowledge about BSE, and all TSEs, increases -- and the science in this area is growing rapidly -- FDA will continue to review this new evidence and steer a course that maintains high standards for food safety in this country.

II. CJD AND PROTECTION OF THE BLOOD SUPPLY

The history of TSE raises questions regarding the transmissibility of CJD through human tissue. While there are no recorded cases of CJD transmission in humans through blood, there

is a theoretical possibility for transmission and FDA has taken aggressive actions to significantly mitigate that potential risk.

The blood supply plays a critical role in the American health care system. While the U.S. has one of the safest blood supplies in the world, it is a formidable task to keep it so. Each year, approximately 12 million units of blood are drawn from volunteer donors for use by more than 3.5 million Americans. Much of this blood, and an additional 12 million units of plasma, is processed into further products, referred to as derivatives, such as immune globulin, used to prevent infections, and clotting factors, such as antihemophilic factor, used to treat bleeding disorders.

Because blood donors may harbor undetectable or undetected communicable disease, blood can transmit disease. Because of this risk, and the fact that millions of Americans depend on blood and blood products, efforts to ensure the safety of the blood supply are a high priority for FDA. One of the challenges such efforts entails is application of current, but incomplete and emerging scientific knowledge, in the decisions about how best to protect public health. CJD presents such challenges.

Background/History of CJD

CJD is a rare but invariably fatal, degenerative neurological disease believed to be associated with a transmissible agent. Cases arise spontaneously at low frequency for unknown reasons; perhaps acquired by external exposure to infectious material; or may arise spontaneously at higher frequency in persons with certain genetic mutations. CJD affects approximately one person to two person per million per year worldwide. From 1979 through 1994, CJD was recorded as a cause of death in 3,642 deaths in the U.S.; representing a stable incidence. (CDC Dispatches, *Emerging Infectious Diseases*, Vol. 2, No. 4, October-December 1996). The clinical latency of CJD can exceed thirty years, although the incubation period is shorter for the known iatrogenic cases.

The nature of the transmissible agent for CJD is not established, but seems to be highly resistant to the current methods of viral inactivation employed with plasma derivatives. The disposition of the agent during fractionation of various plasma derivatives is not presently known.

Between 1983 and 1997, approximately 300 million units of blood and plasma were donated. From 34 reports received (with some reports containing information on more than one donor), 37 donors were either subsequently diagnosed with CJD or deferred based on

concerns with CJD. Of the 37 blood/plasma donors, 25 were reported as subsequently diagnosed with CJD; four had a family member who was diagnosed with CJD; four had received Human Pituitary-Derived Growth Hormone (HGH); and, four had received a dura matter transplant.

The available basic scientific and applied epidemiological data provide no evidence of transmission of CJD via blood transfusion in humans. Moreover, transmission by intravenous infusion of whole blood from CJD patients has not been demonstrated in subhuman primates. The disease, however, has been verified to be transmitted between humans by transplantation of corneas and cadaver dura mater grafts from affected individuals, by use of contaminated EEG electrodes, by certain neurological procedures and by injections of HGH. (CDC Dispatches, *Emerging Infectious Diseases*, Vol. 2, No. 4, October-December 1996). (It should be noted that HGH is no longer used having been replaced by a recombinant-DNA derived alternative product.) In addition, the disease has been transmitted to rodents in laboratory experiments by injecting the buffy coat component of blood from an affected patient into the rodent brain. Although CJD has occurred in transfused patients, we stress that there has <u>not</u> been a documented case of CJD being transmitted through a blood

transfusion. Moreover, there has not been an identified case of hemophiliac death from CJD.

We know that despite our best efforts blood and blood products will never be totally risk free, but we continue to work to achieve optimal safety and availability. While our current knowledge of blood-borne diseases has improved significantly over the past 10-15 years, current scientific knowledge is still incomplete. For example, there is currently no serum test capable of detecting CJD infection.

The fact that there are no documented cases of blood or blood product transmission of CJD in humans does not end the inquiries into the disease nor does it mean that FDA and other agencies and research entities can be complacent. Basic and applied research into the infectious processes of CJD continue to serve as the catalyst for the evolution of FDA policy. We cannot let the absence of scientific information paralyze us.

FDA Regulatory Response

The development of FDA regulatory policy with respect to blood products that could possibly carry a risk of the disease CJD has been vigorous and is ongoing. As clinical and epidemiological knowledge of CJD has increased, FDA has responded aggressively by

reviewing and modifying its policy. Throughout this process, FDA has worked closely with both CDC and NIH, among others, in determining the most appropriate regulatory course of action. Extensive public discussion with all segments of those affected - recipients of products, medical professionals, academicians and industry -- has been conducted throughout FDA deliberations.

FDA Actions Related to Blood and Blood Products

FDA involvement in addressing the possible impact of CJD on the nations's blood supply began with the early awareness of possible transmission. On November 25, 1987, FDA issued a "Memorandum to All Blood Establishments" entitled "Deferral of Donors Who Have Received Human Pituitary-Derived Growth Hormone." This document recommended that all persons who received HGH be barred permanently from donating blood or plasma.

For the period 1983-1992, there were only four reported blood donors who had a confirmed diagnosis of CJD reported post-donation. In response, the blood and plasma product manufacturers initiated a voluntary withdrawal of in-date products that had been prepared from donations from these individuals. In December 1993 FDA expanded its position and issued recommendations for more complete reporting of "post donation information" related to safety.

Partly as a result of these FDA policy recommendations, in late 1994 and early 1995 FDA began receiving additional reports of CJD affected individuals who had donated blood and plasma. At FDA's request, the manufacturers placed in-date, licensed, injectable derivatives (of blood and plasma), as well as intermediates (those products used in further processing), into quarantine awaiting development of FDA recommendations on the use of implicated material.

At the Blood Products Advisory Committee (BPAC) FDA presented data regarding the biology of CJD and case histories of CJD-related donor deferrals and product withdrawals on December 15, 1994. In March 1995, BPAC was again updated on CJD. BPAC was presented with the available scientific information and options for action. BPAC was unable to reach consensus decisions on all of the issues related to product disposition and recipient notification.

FDA, in an effort to further develop its policy on CJD, and because of the outstanding issues that required additional public discussion and consideration, formed a Special Advisory Committee on Creutzfeldt-Jakob Disease and presented information to it on June 22, 1995. The Special Advisory Committee agreed that:

- there was no scientific evidence that CJD is transmitted by transfusion of blood products or by administration of plasma

derivatives;

- implicated blood components should be withdrawn;
- implicated plasma derivatives should be withdrawn; and
- if implicated blood components and/or plasma derivatives are to be released for transfusion, these products should bear special warning labels.

Within two months, after considering these deliberations and extensive internal discussion, FDA issued an interim policy in a memorandum dated August 8, 1995, regarding blood products and plasma derivatives. This further broadened its guidance on donor exclusions for CJD risk and called for withdrawal of implicated blood products. A provision was made for release of affected products in case of a documented shortage provided that the products carried a special label.

In an effort to further expand the knowledge of CJD, FDA and NIH's National Heart, Lung, and Blood Institute held a CJD Workshop on Design of Experimental Studies of Transmission of CJD. The FDA also held many discussions at BPAC on product warning labels.

To avoid the disposal of safe and effective products while protecting public health and safety, FDA consulted extensively with experts in the field of TSEs on the familial nature of some

CJD cases and appropriate use of genetic testing to clarify risk. The Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC) (formally known as the Special Advisory Committee on Creutzfeldt-Jakob Disease) met a second time on July 2, 1996, and discussed refinements to the August 1995 policy. These included the option of reentering deferred donors based on genetic testing results and the disposition of plasma derivatives prepared from product collected from donors with only a single family member diagnosed with CJD. Also, in November 1996, FDA, in cooperation with others, held two public meetings/workshops. Notification procedures to be utilized for implicated products were considered.

FDA revised its recommendations for CJD in a memorandum to manufacturers on December 11, 1996, based on opinions of the advisory committees, public discussion, FDA internal deliberations and discussions with other agencies. The December 11 memorandum updated and superseded the FDA memoranda of August 8, 1995 and November 25, 1987.

FDA, in its December 11 Memorandum, reiterated that the assessment of CJD risk in the donor is a critical responsibility of the blood establishments. In particular, FDA emphasized that family history of CJD requires careful investigation. FDA has

recommended that a family history of CJD should be confirmed by a physician and documented on the basis of currently accepted diagnostic procedures. Also, familial risk, in the context of a donor, applies only to blood relatives of non-iatrogenic cases.

The cautious approach the FDA has taken on CJD related to blood products also affects other products. There are estimated to be over 500 products which use plasma products/derivatives either in manufacturing or formulation. Plasma for manufacturing comes from approximately 25 million donations of blood and plasma derived from about 10 million blood and plasma donors per year. Over a ten year period, 1984-1993, plasma fractionation capacity worldwide increased 61 percent. (Robert, *Journal of the American Blood Resources Association*, at 75, Vol. 4, No. 3 1995).

There is ongoing discussion being conducted by FDA and others concerning the level of risk of CJD transmission in plasma derivatives and blood components. Experiments to quantify this risk are being undertaken by the government and the blood industry. However, it is likely to take several years before conclusive results are obtained. Most scientists believe that any risk from plasma derivatives must be significantly less than from whole blood components.

Despite this inability to more precisely quantify the nature of the risk, as a precaution, FDA has recommended that Source Plasma and plasma derivatives, prepared from donors who are at increased risk for developing CJD, should be quarantined and destroyed. FDA has made an exception from this quarantine for the plasma derivatives, i.e., albumin, immune globulin, etc. (licensed, injectable products), prepared from pools which contain products collected from a donor with only one known family member with CJD. This exception is made because the probability that the case represents familial CJD is low.

FDA has not recommended the quarantine of blood products intended for further research or manufacturing into non-injectable products. FDA has recommended, however, that such products should be labeled with the following statements: 1) "Biohazard"; 2) "Collected from a donor determined to be at risk for CJD"; and, 3) "For laboratory research use only", or "Intended only for further manufacture into non-injectable products".

In the circumstances of a donor with CJD or at increased risk for CJD, consignee notification is recommended to permit recipient tracing and notification as deemed medically appropriate. Given the limited current knowledge about CJD as it relates to blood safety, FDA has made only a few general

recommendations about "lookback" notification. In the event that a donor gives a history of only one known family member with CJD, FDA does not recommend notification of consignees of plasma derivatives or expired blood components.

FDA policy on protection of the blood supply from the remote possibility of CJD transmission has been developed as knowledge and data has evolved. The recommendations for donor deferral, product disposition, and recipient notification have been developed based on a consideration of risk in the donor, risk from the product, and the potential impact on blood product availability. Given the significant size of the population using these products, it is appropriate for FDA to consider the impact of withdrawal from distribution of plasma products in its risk benefit analysis from the perspective of both the effect on the supply of products and the benefit to potential recipients of the products. In its decisions, FDA attempts to balance the need for the products and the risk of using the products.

FDA Decision Making: Case Study

The application of FDA policy in situations involving CJD is evidenced by a recent case. FDA was notified that the certain lots of anti-hemophilic products were manufactured using an ingredient, which had been prepared from pooled plasma,

containing a unit from a blood donor who later died of CJD. These particular anti-hemophilic products had not been released (for distribution) nor approved for release by FDA at the time of the notification to FDA.

In this case, FDA was faced with evaluating the potential risk of CJD in the final products; determining whether FDA should approve release of the lots; and, if released was approved, should any type of notification be provided.

FDA requested a risk assessment from the company which concluded that the risk of CJD in the product was negligible. This risk assessment was reviewed internally and independent risk assessments were obtained from CDC, NIH and Johns Hopkins University. All agreed that the risk, if any, was likely to be remote and considered "vanishingly small" in one analysis. An assessment also was made of the impact on the supply of purified factor VIII available for recipients if the product was not released. The conclusion, based on the scientific analysis and all available, relevant data, was that there was a remote risk of CJD and the products were suitable for release. FDA requested, however, that the situation be conveyed to the affected community -- the hemophilia organizations. The company informed the hemophilia groups. The groups released information on the situation in a community newsletter and other sources.

FDA continues to develop its policy and evaluate the safety of products that have had exposure to an implicated plasma derivative (usually transferrin or albumin) during manufacturing or formulation as new data and information are available.

Adequacy of FDA Response

Although FDA's regulatory response to CJD was initiated long before 1995, the recommendations and comments of the Institute of Medicine (IOM) in its 1995 report could be considered as a framework for evaluating FDA's actions concerning the possible CJD transmission in the blood supply. In its 1995 report *HIV and the Blood Supply: An Analysis of Crisis Decisionmaking*, the IOM concluded that FDA had "missed opportunities" for action in addressing the potential for HIV infection in the blood supply and had chosen "the least aggressive option that was justifiable." The report acknowledged that previous decisions were made "in the context of great uncertainty" given the science. When "knowledge is imprecise and incomplete," however, IOM recommended that there should be "a more systematic approach to blood safety regulation when their [sic] is uncertainty and danger to the public."

The IOM made several recommendations directed specifically at FDA which mirror FDA's actions in developing responses to possible CJD transmission through the blood supply.

Recommendation 6 of the IOM report stated:

> Where uncertainties or countervailing public health concerns preclude completely eliminating potential risks, the FDA should encourage, and where necessary require, the blood industry to implement partial solutions that have little risk of causing harm.

Recommendation 7 of the IOM report stated:

> The FDA should periodically review important decisions that it made when it was uncertain about the value of key decision variables.

FDA has undertaken to incorporate these recommendations into its decision making and oversight of the nation's blood supply. The discussion of FDA's actions taken in response to the concerns raised by possible CJD transmission illustrate that FDA has benefited from past lessons and has responded to the challenge of dealing with uncertain risks that could impact the safety and availability of blood and plasma products.

This Committee also made recommendations in its report *Protecting the Nation's Blood Supply From Infectious Agents: The Need For New Standards To Meet New Threats* (House Report 104-746, August 2, 1996). In response to the Committee's concerns, FDA has provided enhanced public access concerning recalls and withdrawals of blood and blood products; increasing public input in the discussion regarding policy development on withdrawals and notification of plasma products; and, continuing research into the risk factors associated with pool size of donors.

FDA has made information concerning recalls and withdrawals widely available to interested and affected parties. A voice information system with toll free lines has been set up with information on fractionated product recall and market withdrawal information. A fax information system has been put into place allowing "fax-on-demand." The FDA Home Page contains the recall and withdrawal information and an automated e-mail system has been established to distribute information to those persons desiring information not only on recalls and withdrawals but all blood related public documents.

CONCLUSION

FDA continually strives to make the food and blood supply safer. We will continue to evaluate new studies, scientific and epidemiological data on TSEs and apply that knowledge to FDA policy. We look forward to working with the Committee on these issues.

Mr. SHAYS. Dr. Detwiler.

Dr. DETWILER. Good afternoon, Mr. Chairman, Members. Thank you very much for giving me this opportunity to appear before the subcommittee to discuss the Animal and Plant Health Inspection Service's, or APHIS, efforts to prevent our Nation's cattle from becoming infected with bovine spongiform encephalopathy, BSE.

As you've announced, my name is Linda Detwiler. In addition to serving as APHIS's Area Veterinarian in Charge for New Jersey, I also chair the APHIS TSE working group.

Mr. Pappas, I just want you to know that even though New Jersey, we have the nickname the Garden State, most people don't think of us as that, but I grew up on a farm. My dad still has a farm, and I keep a couple of Jersey cows that are big, fat, and happy.

Mr. PAPPAS. If I could, Mr. Chairman, just to mention, I come from the 12th District of New Jersey, which I am told from the New Jersey Farm Bureau is the largest cattle producing district in the State of New Jersey; 26 head. I know that is relative compared to other States.

Dr. DETWILER. With me today is Dr. Glenn Morris of the public health division of USDA's Food Safety and Inspection Service to assist me with questions that might pertain to FSIS.

APHIS is a part of the U.S. Department of Agriculture's Marketing and Regulatory Programs mission area. Our primary responsibility is to protect the health of U.S. agriculture from foreign animal and plant diseases and pests that could adversely impact production and hamper the health of our Nation's livestock. This ensures that our Nation's crops, poultry, and livestock are marketable both domestically and overseas.

In carrying out this mission, APHIS closely monitors the agricultural health situations of our trading partners; regulates the importation of animals and animal products based on the potential risk of agricultural disease or pest introduction; and conducts ongoing surveillance programs to ensure that no diseases or pests of concern have slipped past our defenses. In the event of an outbreak, APHIS is poised to immediately implement emergency response efforts. Working together with the industry and other State and Federal agencies, we provide a nationwide agricultural health infrastructure.

To reiterate, BSE has not been detected in the United States, and USDA has worked aggressively and proactively to keep it that way. The measures APHIS has taken in this regard include prohibitions and/or restrictions on certain animal and product imports; ongoing surveillance for signs of the disease in the United States; preparation of an emergency response plan in the unlikely event an introduction were to occur; and ongoing educational efforts.

APHIS has formed a TSE working group, which is composed of an agency pathologist; an epidemiologist; veterinarians from our import-export; emergency programs; and international services staffs; three of our field veterinarians, including myself; and a public affairs specialist.

Our group continually monitors and assesses all ongoing events and research findings regarding spongiform encephalopathies, as new information and knowledge may lead to revised conclusions

about risk, pathology, and improved diagnostic and prevention measures.

The working group also disseminates information about TSEs and serves as a reference source for questions about these diseases. In doing this, we have actively shared information and coordinated closely with each of the Federal agencies represented here today, as well as the States, the livestock and affiliated industries, veterinary and research communities, and consumer groups. Together, all of us are working to ensure that the Federal approach to TSEs is based on the most up-to-date and sound scientific data available.

Before I begin to discuss our program to exclude BSE from the United States, I would like to begin with some background on the status of TSEs in this country.

The primary TSE known in this country is scrapie. It was first diagnosed in the United States in sheep and goats in 1947, and since 1952 the United States has had some form of eradication and control for the disease. Since 1992, these efforts have taken the form of a nationwide scrapie flock certification program and interstate movement restrictions on sheep and goats from infected and source scrapie flocks.

The intent of the program is to monitor flocks over a period of 5 years or more and certify for health and marketing purposes those that have not displayed evidence of scrapie, and another aspect of the program is to prohibit the movement of high risk animals from scrapie flocks in interstate commerce. Scrapie has existed in some countries, most notably Great Britain, for centuries, and sheep with the disease have never been shown to pose a direct risk to human health.

Currently, APHIS is working with the sheep industry to reexamine our program and make adjustments as needed to both the regulations and certification programs. We're also working to develop a national effort of active scrapie surveillance using the most recent diagnostic techniques. If this effort is successful, we will be the first Nation in the world to achieve this end.

I can also speak on a personal nature. APHIS provides a lot of samples for the research community. Like Dr. Joe Gibbs, I've selected cerebrospinal fluid samples, I've collected tonsil biopsies. That's a little more difficult, as the sheep don't want to open their mouths and say "ahh" too easily.

In 1989, APHIS banned all live cattle and other ruminants and restricted the importation of most cattle products from Great Britain, which at that time was the only country known to have BSE. As other countries have reported BSE in native cattle, they have become subject to these same restrictions.

In 1991, APHIS formalized these restrictions with regulations. Under these regulations, certain products cannot be imported into the United States, except under special permit for scientific, educational or research purposes or under certain conditions. These products include serum, meat-and-bone meal, bone meal, blood meal, offal, fat, glands, and collagen. Gelatin derived from ruminants from BSE countries is currently prohibited entry into the United States for use in animal feeds or for any purpose that would result in contact with ruminants. All these were enacted to

protect the health of U.S. livestock and safeguard our human population as well.

APHIS has a comprehensive surveillance program in the United States to ensure swift detection and control in the unlikely event BSE introduction occurred.

To ensure that we would be able to identify BSE readily if it were to appear in the United States domestic cattle herd, we sent USDA pathologists to Great Britain after the disease was first identified in 1986. Our goal was to learn directly from our British counterparts about the pathology of the disease and diagnostic techniques. In addition, USDA has trained over 250 Federal and State field veterinarians throughout the United States and several of our diagnosticians have spent time in Great Britain in an effort to learn from that country's experience in the disease.

USDA's Food Safety and Inspection Service performs pre-slaughter inspections at all federally inspected slaughter establishments, and their inspectors are on the alert for animals that appear to have central nervous system disorders. Any animals exhibiting neurological signs similar to those seen with BSE are condemned, and their brains are submitted to APHIS's National Veterinary Services Laboratories for analysis. In addition, private veterinarians refer neurologic cases to us directly from the farm or from veterinary schools.

Since 1990, more than 60 diagnostic labs throughout the United States and USDA's National Veterinary Services Laboratories have examined thousands of cattle brains submitted from adult cattle displaying neurologic disease signs either at slaughter or on the farm. I provided in my written testimony the number of brains submitted. I've updated that. As of January 23d, we've examined 5,342 brains with no evidence of BSE.

We've also provided veterinary practitioners, lab diagnosticians, and inspectors with information to assist them in recognizing the clinical signs of BSE, and I really want to emphasize this, the importance is we educate producers on what to look for and where to report it. That is one of the best methods also of surveillance, and I think APHIS has really tried to concentrate our efforts in this education.

In the unlikely event we have a BSE occurrence, we have developed an aggressive emergency action plan to deal with the animal health and public health issues. The plan includes immediately informing Congress, concerned State and Federal agencies, the livestock industry, consumer groups, and the general public about the implications of such an outbreak and what we would be doing to respond in terms of handling the animals and animal products, and in the area of surveillance, if this is committed, to continually work with researchers both in the United States and abroad to update our diagnostic techniques, which is a key to us for surveillance. The education, as I stated earlier, is critical. We have developed training materials, video we have obtained from the United Kingdom. I've submitted those to your committee for information, video on scrapie, BSE, fact sheets on those two diseases and chronic wasting disease.

Although BSE has not been diagnosed in the United States, we support the Food & Drug Administration's effort to provide an ad-

ditional safety net by banning certain products in ruminant feed. We are currently continuing to review that proposal carefully and we will submit formal comments on its specific provisions as part of the rulemaking record.

Mr. Chairman, members of the committee, thank you for providing us the opportunity to alleviate public concern about any risk of BSE introduction into the United States. By taking the necessary precautions to prevent known risks such as importing infected cattle or cattle products, as well as other potential risks such as introduction and amplification of the agent in the cattle food chain, we are protecting the cattle population. And a BSE-free cattle population safeguards all of us as consumers against the possibility of a human health risk.

And may I ask, I brought a simple diagram——

Mr. SHAYS. Sure. This will be concluding your comments?

Dr. DETWILER. Yes.

Mr. SHAYS. You know, what I am going to ask you to do is maybe just turn that mike that is up there and see if you could speak somewhat toward there so it is part of the record. At least kind of project your voice that way.

Dr. DETWILER. This diagram will——

Mr. SHAYS. I am asking you to do something impossible, I am sorry.

Dr. DETWILER. Yes, sorry.

Dr. FRIEDMAN. Would you like me to point and you can just speak?

Mr. WAXMAN. Mr. Chairman, there is a court reporter, so we don't have to get a recording.

Mr. SHAYS. Are you picking it up?

The REPORTER. Yes.

Dr. DETWILER. The known risks of BSE would be the foreign sources of BSE. In 1989, APHIS took the precautions to shut that off. So we have a protection against the cattle population. That's a known risk against an introduction.

Now, the unknown or the unquantified risks and the potential risks would be a spontaneous case occurring in cattle or some link with sheep, and the two theories for the origin of BSE is it came from scrapie infected sheep incorporated into the rendering chain, and by some change in the rendering, got into a cattle feed ration, and then the feed fed back to the general population. The other is from a spontaneous case occurring in a cow, through the feed chain with rendering, changes in rendering process incorporated into the general population through feed into the feed supply in a country and through into the U.S. cattle population. And with the FDA's proposed regulation on the ruminant feed, that would prohibit this into the United States, thereby shutting off both the known risks of BSE as well as the unquantified or possible risks. And then by protecting the U.S. cattle population, that would protect the human population for the use of cattle products.

And I would just like to say, too, one thing on a personal note. In 1985, I took the job—I left private practice to take the job with the government and I had some hesitation to do that because of perceptions of family, you know, government employees, and friends and colleagues, and because of personal reasons I said I will

do this for a year. I got involved with scrapie early on and I worked in the agency to control and eradication and surveillance of scrapie. Early on with BSE I got involved with the agency's preventive actions. All along with these efforts, I am here to tell you I am not high up in the department, I am not high up in APHIS. I've been involved in the day-to-day dog fights with these programs and the disease, and the thing that made me stay these number of years are the people I worked with, not only in the agency, the people like my colleagues in APHIS and like Dr. Gibbs, that give me their phone number and say call me any time day or night, or if there's something we need to know on a day off will go into the office and fax me some research. People in the industry that are willing, saying what do we need to do. The sheep industry, people that sat at their table and cried because of the loss of their flocks, said we'll donate our flock to research. Those people. International colleagues that we share frustrations, and I have family in all these places.

So from my 1985 to 1986 game plan, I am here to tell you in 1997 I am still here because I am proud now to say that I am a Federal employee, I am proud really to say that I work for APHIS, who is an agency that is not complacent, and I work with a lot of good colleagues. So hopefully when you call me back in 20 years when I am ready to retire, I will say the same thing.

[The prepared statement of Dr. Detwiler follows:]

TESTIMONY OF DR. LINDA A. DETWILER
CHAIR, TSE WORKING GROUP
ANIMAL AND PLANT HEALTH INSPECTION SERVICE
U.S. DEPARTMENT OF AGRICULTURE
BEFORE THE
U.S. HOUSE OF REPRESENTATIVES
COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT
SUBCOMMITTEE ON HUMAN RESOURCES
JANUARY 29, 1997

Mr. Chairman, I appreciate this opportunity to appear before the Subcommittee to discuss the Animal and Plant Health Inspection Service's (APHIS) efforts to prevent our Nation's cattle from becoming infected with bovine spongiform encephalopathy (BSE). My name is Dr. Linda Detwiler, and, in addition to serving as APHIS' Area Veterinarian in Charge for New Jersey, I chair APHIS' working group on the family of diseases to which BSE belongs: transmissible spongiform encephalopathies, or TSEs.

Introduction

APHIS is a part of the U.S. Department of Agriculture's (USDA) Marketing and Regulatory Programs mission area. Our primary responsibility is protecting the health of U.S. agriculture from foreign animal and plant diseases and pests that could adversely impact production. This ensures that our Nation's crops, poultry, and livestock are marketable both domestically and overseas. In carrying out this mission, APHIS closely monitors the agricultural health situations of our trading partners; regulates the importation of animals and animal products based on the potential risk of agricultural disease or pest introduction; and conducts ongoing surveillance programs to ensure that no diseases or pests of concern have slipped past our defenses. In the event of an outbreak, APHIS is poised to immediately implement emergency response efforts. Working together with industry and other State and Federal agencies, we provide a nationwide agricultural health infrastructure.

BSE has not been detected in the United States, and USDA has worked aggressively and proactively to keep it that way. The measures APHIS has taken in this regard include prohibitions and/or restrictions on certain animal and product imports; ongoing surveillance for signs of the disease in the United States; preparation of an emergency response plan in the unlikely event an introduction were to occur; and ongoing educational efforts. APHIS has formed a TSE working group, which is composed of an Agency pathologist; an epidemiologist; veterinarians from our import-export, emergency programs, and international services staffs; three of our field veterinarians, including myself; and a public affairs specialist. Our group continually monitors and assesses all ongoing events and research findings regarding spongiform encephalopathies, as new information and knowledge may lead to revised conclusions about risk and pathology and improved diagnostic and prevention

measures. The working group also disseminates information about TSEs and serves as a reference source for those with questions about these diseases. In doing this, we have actively shared information and coordinated closely with each of the other Federal agencies represented here today, as well as the States, the livestock and affiliated industries, veterinary and research communities, and consumer groups. Together, all of us are working to ensure that the Federal approach to TSEs is based on the most up-to-date and sound scientific data available.

Status of Other TSEs in the United States

Before I discuss our program to exclude BSE from the United States, I would like to begin with some background on the status of other TSEs in this country.

The primary TSE known to occur in this country is scrapie, which was first diagnosed in U.S. sheep and goats in 1947. Since 1952, the United States has had some form of an eradication or control program in place for this disease. Since 1992, these efforts have taken the form of a nationwide voluntary scrapie flock certification program and interstate movement restrictions on sheep and goats from infected flocks. The intent of the program is to monitor flocks over a period of 5 years or more and certify for health and marketing purposes those that have not displayed evidence of scrapie. Scrapie has existed in some countries--most notably, Great Britain--for centuries, and sheep with the disease have never been shown to pose a direct risk to human health. However, because some studies indicate a potential health risk for cattle and other ruminants that consume feeds containing proteins from rendered scrapie-infected sheep, the FDA has gone forward with the proposal we are discussing today.

Another TSE that occurs in this country is known as chronic wasting disease, which affects deer and elk in limited areas of Colorado and Wyoming. APHIS and USDA's Agricultural Research Service have assisted State wildlife and veterinary diagnostic officials in the development of diagnostic techniques and research data.

Finally, there are also TSEs known to affect mink and felines. The last known case of the TSE that affects mink occurred in the United States in 1985, although there were several cases that occurred before 1964. The TSE that affects felines has never been detected in the United States.

Import Restrictions to Prevent the Entry of BSE

In 1989, APHIS banned all live cattle and other ruminants and restricted the importation of most cattle products from Great Britain, which at that time was the only country known to have BSE. As other countries have reported BSE in native cattle, they have become subject to these same restrictions.

In 1991, APHIS enacted restrictions on the importation of ruminant meat and edible products and banned most byproducts of ruminant origin from countries where BSE is known to exist.

Under these regulations, certain products cannot be imported into the United States, except under special permit for scientific, educational, or research purposes, or, under certain conditions, to be used in cosmetics. These products include serum, bone meal, meat-and-bone meal, blood meal, offal, fat, glands, and collagen. Gelatin derived from ruminants from BSE countries is currently prohibited entry into the United States for use in animal feeds or for any purpose that may result in contact with ruminants. All of these measures to protect the health of U.S. livestock have served to safeguard human health as well.

Surveillance for BSE

APHIS has a comprehensive surveillance program in place in the United States to ensure timely detection and swift response in the unlikely event that an introduction of BSE were to occur.

To ensure that we would be able to identify BSE readily if it were to appear in the U.S. domestic cattle herd, we sent USDA pathologists to Great Britain after the disease was first identified there in 1986. Our goal was to learn directly from our British counterparts about the pathology of the disease and diagnostic techniques. In addition, USDA has trained over 250 Federal and State field veterinarians throughout the United States in recognition of BSE, and several of our diagnosticians have spent considerable time in Great Britain in an ongoing effort to learn from that country's experience with this disease.

USDA's Food Safety and Inspection Service (FSIS) performs pre-slaughter inspections at all federally inspected slaughter establishments, and their inspectors are on the alert for animals that appear to have central nervous system disorders. Any animals exhibiting neurological signs similar to those seen with BSE are condemned, amd their brains are submitted to APHIS' National Veterinary Services Laboratories for analysis. Private veterinary practitioners around the country refer neurologic cases to us either directly or through veterinary schools or State diagnostic laboratories.

Since 1990, more than 60 veterinary diagnostic laboratories across the United States and USDA's National Veterinary Services Laboratories have examined thousands of cattle brains submitted from adult cattle displaying neurologic signs either at slaughter or on the farm. As of December 31, 1996, a total of 5,211 brains from 47 States and Puerto Rico had been examined with no evidence of BSE detected.

We have provided veterinary practitioners, veterinary laboratory diagnosticians, veterinary inspectors, and producers around the country with information to assist them in recognizing the clinical signs of BSE. We have emphasized the vital importance of early reporting of suspect cases and publicized the proper reporting channels.

To ensure that we have centralized data on our findings, we have established a special database containing the results of all histologic examinations for BSE as well as other information on

neurological conditions in cattle. We also use other databases on animal health conditions, including information collected through the national Veterinary Diagnostic Laboratory Reporting System. This system is a cooperative effort of the American Association of Veterinary Laboratory Diagnosticians, the United States Animal Health Association, and APHIS.

Because BSE-like encephalopathies have been diagnosed in seven species of exotic bovidae at zoos in England, veterinary pathologists at zoos in the United States routinely conduct post mortem examinations on the brains of zoo animals exhibiting neurologic signs.

In the unlikely event that we had a BSE occurrence in this country, we have developed an aggressive emergency action plan to deal with the animal health and public health issues. The plan includes immediately informing Congress, concerned Federal and State government agencies, the livestock industry, consumer groups, and the general public about the implications of such an outbreak and what we would be doing to respond.

Education on BSE

A critical component of our efforts to deal with BSE is the information and training we provide to veterinary practitioners on the clinical signs and diagnosis of BSE and the procedures for sample submission to our laboratories. As I stated earlier, over 250 Federal and State veterinarians throughout the United States have been trained in the recognition of this and other foreign diseases, with several of our diagnosticians spending considerable time in Great Britain learning from the experience of their counterparts there. We have developed training and information materials for use not only by these government veterinarians but also by private practitioners, diagnostic laboratories, and the cattle industry. These materials range from fact sheets and risk assessment studies to videotapes of British cattle showing clinical signs and microscope slides showing typical BSE lesions. APHIS experts have actively participated in and made presentations at international seminars as well as conferences and meetings sponsored by various animal health organizations in the United States. We have also sponsored several forums for information sharing among Federal and State governments, the industry, and the research community.

Ruminant-to-Ruminant Feeding

Although BSE has never been diagnosed in this country, we support the Food and Drug Administration's effort to provide an additional safety net by banning the use of ruminant- and mink-derived proteins in ruminant feed products. We are currently continuing to review this proposal carefully, and we will submit formal comments on its specific provisions as part of the rulemaking record.

Conclusion

Mr. Chairman, thank you for providing us the opportunity to alleviate public concern about any risk of BSE introduction into the United States. By taking the necessary precautions to prevent *known* risks such as importing infected cattle or cattle products as well as other potential risks such as introduction and amplification of the agent in the cattle food chain, we are protecting the cattle population. A BSE-free cattle population safeguards all of us as consumers against the possibility of a human health risk.

This concludes my prepared testimony. I would be pleased to answer any questions you may have.

Mr. SHAYS. Well, we're proud to have you here and hopefully when we do that, maybe you will be running one of those agencies in 20 years.

We have now Dr. Schonberger, and we welcome your testimony. Thank you, Dr. Detwiler.

Dr. SCHONBERGER. Good afternoon. I am Lawrence Schonberger, from the Centers for Disease Control and Prevention. I coordinate CDC's surveillance on Creutzfeldt-Jakob disease, CJD. I am accompanied by Dr. Rima Khabbaz and Dr. Bruce Evatt. We are pleased to discuss CDC's role in two public health issues about CJD: First, whether a possibly new variant form of CJD reported in the United Kingdom may represent food-borne spread to humans of bovine spongiform encephalopathy; and second, whether CJD may pose a risk to blood safety. To help in the assessment of both these issues, CDC gathers and interprets surveillance data about CJD.

Bovine spongiform encephalopathy was first diagnosed in 1986 as part of an ongoing outbreak in cattle in the United Kingdom. Although there is no general agreement among investigators about the original source of this outbreak, or epizootic, there is general agreement that feeding rendered bovine meat and bone meal to young calves amplified the spread of this disease. Indeed, the key control measures which were directed in eliminating the use of ruminant protein for ruminant feed, what we're discussing today had a marked beneficial effect.

Based on 10 persons with onset of an apparently new variant form of CJD in 1994 and 1995, an advisory committee in the United Kingdom announced its concern just last March that these patients could represent the beginning of an epidemic in humans that might parallel the course of the epizootic of the bovine spongiform encephalopathy, but delayed a few years. Shortly thereafter, consultants called for the establishment of worldwide surveillance programs for both bovine spongiform encephalopathy and the newly recognized form CJD.

In the United States, as you've just heard, the USDA has reported no evidence of the cattle disease and CDC has found no evidence for the occurrence of the human disease. CDC's surveillance efforts for the new variant CJD have included ongoing reviews of national mortality data, an active surveillance effort in CDC's emerging infections programs, ongoing reviews of hospital records of patients under 55 years of age identified through national mortality data in collaboration with State health departments, and a new collaboration with the American Association of Neuropathologists to obtain reports of suspected cases of the new variant CJD regardless of age or initial clinical diagnosis.

In my written testimony I explained why I believe the evidence now is strong that the newly described variant represents a novel form of CJD. Whether this novel variant is causally linked to bovine spongiform encephalopathy, however, is less clear. Although the accumulating evidence for such a link is increasing, continuing surveillance of CJD and bovine spongiform encephalopathy in many countries, including the United States, and especially in the United Kingdom, will be critical for determining whether and to what extent the agent of bovine spongiform encephalopathy may be causing disease in humans.

In the meantime, because of the general acceptance that ruminant-to-ruminant feed played a role in amplifying bovine spongiform encephalopathy in the United Kingdom and because of the risk of the possible transmission of this cattle disease to humans, CDC continues to support FDA's proposal to modify or end this cattle feeding practice in the United States.

CDC surveillance data have also been used to examine where CJD may pose a risk to blood safety. Although some laboratory experimental studies support concern about such a risk, epidemiologic data indicate that this risk, if present, must be low. Published case control studies and limited followup data on patients who received blood units from a CJD donor, for example, have not indicated an increased risk of CJD in blood recipients. The 3,642 cases of CJD in the United States reported through CDC's mortality system, 1979 through 1994, demonstrated stable annual rates of this disease. Thus, despite regular blood donations by donors who subsequently developed CJD, blood transfusions do not appear to be amplifying CJD infections in the population.

In addition, none of these several thousands cases of CJD were reported also to have had hemophilia, thalassemia or sickle cell diseases, diseases with increased exposure to blood or blood products. Because clotting factor concentrates used by hemophilia patients to control bleeding are commonly derived from 4,000 to 30,000 blood donors, CDC has also sought cases of CJD specifically among persons with hemophilia. None have been found.

CDC and the American Red Cross have initiated a study of recipients of transfusible blood components derived from CJD donors. At last report, of the 23 investigated recipients who survived 5 or more years after their transfusion, none had died of CJD. So despite some experimental evidence suggesting a potential for bloodborne transmission of CJD, the accumulating epidemiologic data have strengthened CDC's previous conclusions that the risk, if any, for transmission of CJD by blood products is extremely small and theoretical.

Thank you for the opportunity to discuss these public health issues concerning CJD, and I will be happy to answer questions you or other members of the subcommittee may have.

[The prepared statement of Dr. Schonberger follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30333

STATEMENT OF

LAWRENCE B. SCHONBERGER, M.D., M.P.H.

NATIONAL CENTER FOR INFECTIOUS DISEASES

CENTERS FOR DISEASE CONTROL AND PREVENTION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT

SUBCOMMITTEE ON HUMAN RESOURCES

U.S. HOUSE OF REPRESENTATIVES

JANUARY 29, 1997

Good afternoon. I am Dr. Lawrence B. Schonberger, Assistant Director for Public Health, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC). I am the physician epidemiologist who coordinates CDC surveillance activities on Creutzfeldt Jakob disease (CJD) in the United States. I am accompanied by Dr. Rima Khabbaz and Dr. Bruce Evatt, also with CDC's National Center for Infectious Diseases. We are pleased to be here this morning to discuss with you CDC's role in two evolving public health issues about CJD; (1) whether a possibly new variant form of CJD reported in the United Kingdom may represent foodborne spread to humans of the agent of Bovine Spongiform Encephalopathy (BSE), and (2) whether CJD may pose a risk to blood safety. To help in the assessment of both these issues, CDC gathers and interprets CJD surveillance data. Such data consist primarily of routinely collected national mortality surveillance and special studies of defined subpopulations, such as hemophilia patients.

Both CJD in humans and BSE in cattle, are invariably fatal brain diseases that are classified as transmissible spongiform encephalopathies. The most sensitive and specific, generally available method for confirming these diseases is by pathologic examination of brain tissue. Both are regarded as having the same type of disease; the leading hypothesis for the cause of both these diseases is that they result from the accumulation in affected brains of a transmissible agent known as the "prion

protein," which is an abnormal form of a protein that is found in normal tissues.

BSE AND NEW VARIANT CJD

BSE was first diagnosed in 1986 as part of an ongoing epizootic in the United Kingdom (U.K.). As of mid-1996, more than 160,000 cases of BSE in cattle were confirmed in the U.K. in more than 33,000 herds. BSE cases may have initially resulted from feeding cattle rendered protein, such as meat-and-bone meal, produced either from the carcasses of sheep infected with the transmissible spongiform encephalopathy of sheep, known as scrapie, or from the carcasses of rare, spontaneously occurring, endemic cases of BSE that had not been previously recognized. Although there is no general agreement among investigators about the original source of the BSE epizootic, there is general agreement that feeding rendered bovine meat-and-bone meal to young calves amplified the spread of BSE.

Once the disease was recognized in the United Kingdom, the key BSE control measures instituted included a ban on using ruminant protein for ruminant feeds introduced in July 1988, and a ban on using brain, spinal cord, and other specified bovine offals in feed for non-ruminant animals and poultry, introduced in September 1990. A marked decline in the number of BSE affected animals born in each year after the bans in 1988 and 1990

suggested that these control measures were having a beneficial effect, consistent with the decreasing risk of exposure.

In March 20 1996, an expert advisory committee to the government of the United Kingdom announced its "great concern" that the agent responsible for the BSE epizootic might have spread to humans, based on recognition of 10 persons with onset of an apparently new variant form of CJD during February 1994 through October 1995. The advisory committee's concern raised the possibility that the 10 cases could represent the beginning of an epidemic of the new variant CJD in humans that might parallel the course of the epizootic of BSE in cattle, but delayed by about 5 to 10 years.

The evidence for the existence of the new variant was published in detail in the medical journal, Lancet, on April 6, 1996. The illness is diagnosed based on a newly recognized brain pathologic profile in addition to the usual pathologic findings of classical CJD. In addition to the newly recognized pathologic profile, the unusually young age of the patients (median age at death, 29 years) and several atypical clinical features, including a 1 year or longer median duration of illness, supported the proposal of the authors that a new variant of CJD had emerged.

The 10 patients initially reported with the new variant CJD resided in widely scattered areas of the United Kingdom. Review

of these patient's medical histories, genetic analyses and consideration of other possible causes did not provide an adequate explanation for these cases. Nevertheless, there was also no clear epidemiologic linkage to BSE.

In January 1997, the United Kingdom confirmed variant CJD in 4 additional persons. Seven of the total of 14 new variant CJD cases in the United Kingdom were reported to have had onset of illness in 1994, 6 in 1995 and 1 in 1996. The occurrence of only 1 confirmed case with onset in 1996 should be interpreted keeping in mind the long median duration of illness and the need for brain tissue to confirm the diagnosis.

In April and again in May 1996, consultants meeting at the World Health Organization in Geneva called for establishment of ongoing surveillance programs worldwide to better determine the geographic distribution of both BSE and of the newly recognized variant of CJD and to better clarify the possible relationship of these two diseases.

To date, the only reported non-British person with definite new-variant CJD has been a Frenchman with onset of CJD in 1994 who had traveled outside of France only once and that was to Spain in 1990. The letter in Lancet reporting this patient indicated that he had no particular contact with cattle.

In the United States, the U.S. Department of Agriculture has reported no evidence of BSE in any U.S. cattle. CDC has been seeking evidence for either the presence or absence of the new variant of CJD. In addition to the ongoing reviews of national CJD mortality data, CDC initiated an active surveillance effort for CJD during April and May 1996. This active surveillance was conducted in CDC's Emerging Infections Programs (EIP) in four sites (Connecticut, Minnesota, Oregon and the San Francisco Bay area of California) and in a metropolitan Atlanta site. The EIP conduct special surveillance and laboratory/epidemiologic projects and pilot and evaluate prevention programs. They were established through cooperative agreements between CDC and state health departments with funding provided by Congress to begin implementation of CDC's plan, "Addressing Emerging Infectious Disease Threats: A Prevention Strategy for the United States," published in 1994. The 1993 population for these 5 sites was 16.3 million.

In addition, to improve the sensitivity of surveillance for the new variant CJD, CDC and State Health Departments initiated ongoing followup reviews of clinical and neuropathology records on CJD patients under 55 years of age who are identified through national mortality data. Also, in September 1996, CDC in collaboration with the American Association of Neuropathologists, alerted their members of the importance of reporting any

suspected cases of the new variant CJD, regardless of the patient's age or the initial clinical diagnosis.

The results of the review of the national mortality surveillance were published in the October-December 1996 edition of CDC's journal, "Emerging Infectious Diseases." CDC found no evidence for the occurrence of the new variant CJD in the United States, a conclusion supported also by the ongoing CJD surveillance efforts. The results of the active surveillance effort during last April and May were reported in the August 9, 1996, edition of CDC's "Morbidity and Mortality Weekly Report" (MMWR). Copies of the journal and the MMWR have been provided to the committee.

How strong is the scientific evidence that a new variant of CJD has emerged in Europe and that it is causally linked to BSE? There has been worldwide publicity about the new variant CJD, but there have been no documented cases outside of France and the United Kingdom or anywhere with onset before 1994. Given the negative results of our own surveillance efforts here in the United States, there is strong evidence that the newly described variant represents a novel form of CJD. In addition to the increasing concurrence among neuropathologists that they have not previously seen the pathologic profile of the variant CJD, the extraordinary young age of the patients also indicates the emergence of a novel variant. For example, in contrast to the young median age of the new variant cases that reflects the

occurrence of 5 new variant CJD deaths under 30 years of age, CDC's national mortality surveillance, 1979 through 1994, has shown that the median age for CJD deaths is in the 65 to 69 year old age group. Further, the annual CJD death rate under 30 years old has been practically nonexistent, less than 5 cases per billion.

Whether or not this novel variant is causally linked to the ongoing BSE epizootic in the United Kingdom is less clear, although the accumulating evidence for such a link is increasing. The epidemiologic evidence is consistent with causation, but not strongly supportive. For example, the interval between peak exposure to potentially BSE contaminated food (1985 to 1989) and onset of initial cases (1994-1996) is consistent with known incubation periods for CJD. The absence of confirmed cases of new variant CJD in other geographic areas free of BSE, as indicated, for example, by the CDC surveillance data, supports the existence of a causal link. Among the stronger evidence supporting a causal link are the transmission studies published in late June, 1996, that showed that three BSE inoculated macaques and the new variant CJD had strikingly similar clinical and neuropathological features. More recently, in October 1996, John Collinge and colleagues published in the journal, Nature, on a new molecular marker that showed that the prion proteins from the brains of 10 patients with the new variant CJD had characteristics distinct from other types of CJD and which

resembled those of known BSE infected animals. In January 1997, examination of tonsilar tissue from another deceased patient with the new variant CJD was reported in the journal, Lancet, to have detectable prions with the same molecular marker.

In conclusion, an accumulation of data provide support for, but do not prove, a causal link between BSE and the new variant CJD. The continuing assessment of this link will be greatly assisted by the results of standard strain typing of the agent of new variant CJD in mice, which may become available within the next 15 months. The results of ongoing surveillance of both CJD and BSE in many countries, including the United States and especially in the United Kingdom, will also be critical for this assessment and for determining to what extent the agent of BSE may be causing disease in humans.

In the meantime, because of the general acceptance that ruminant-to-ruminant feed played an important role in amplifying the BSE epizootic in the United Kingdom and because of the current evidence for a possible risk of transmission of BSE to humans, CDC continues to support the Food and Drug Administration's (FDA) proposal published earlier this month to modify or end this animal feeding practice in the United States.

CJD and BLOOD SAFETY

CDC's surveillance data have also helped examine the concern that CJD may pose a risk to blood safety. In October 1994, concern about CJD and blood safety was heightened by a report to the American Red Cross of the occurrence of CJD in a frequent blood donor. As part of the Department of Health and Human Services response to this concern, CDC assessed the risk of transmission of CJD by blood products and concluded, in November 1994 and again in July 1995, that this risk, if it exists, is extremely small and theoretical. The term theoretical was used to describe this risk because no convincing evidence was found for any instance of transmission of CJD to a human recipient by a blood product.

Nevertheless, concerns exist about transmissibility of CJD by blood and blood products because of several characteristics of the disease itself. CJD is an invariably fatal brain disease that is caused by an unconventional agent. Disinfection is unusually difficult. Incubation periods are long, measured in years, and there is no practical screening test to identify those who are incubating the disease.

In addition, since the 1970s, iatrogenic cases of CJD have been increasingly recognized including from a corneal

transplant,contaminated cortical electrodes, dura mater grafts and cadaver derived growth or gonadotropic hormones.

Finally, the most direct reason for concern about the risk of transmitting CJD by blood products are laboratory and experimental studies, particularly those that have demonstrated both (a) the probable, occasional, presence of the CJD agent in the blood of CJD patients at low titer, and (b) the infectivity of blood, most likely the white cell component, throughout most of the incubation period in two different rodent models of CJD. Whether the results of these studies in rodents apply to CJD infections in humans is unknown.

Although the laboratory and experimental studies support some concern about the possible risk of CJD transmission by human blood, epidemiologic data indicate that this risk, if present, must be low.

In August 8, 1995, a letter from Germany in the Lancet journal reported long term followup data on a group of recipients of blood products derived from an identified CJD donor. This letter indicated no evidence of transmission of CJD to either 27 patients who definitely, or eight who probably, received a blood unit from a CJD donor. None of the recipients in either group died of CJD. At least 7 patients who definitely received a blood unit from the CJD donor survived 10 years or longer after the

transfusion, including one who survived afterwards for at least 20 years.

An article published in Neurology 1996, which combined data from Japan, the United States, and the United Kingdom, demonstrated that only 9.8% of 174 patients with CJD compared to 13.7% of 328 control subjects had a history of a blood transfusion. To the extent that transfusions might be a cause of CJD, one would have expected that the proportion of CJD patients with a history of transfusion would have been significantly higher than that in the control subjects.

CDC's national mortality surveillance for CJD and surveillance projects with which CDC is collaborating provide further information about the possible risk of transmission of CJD by blood products. As published in the most recent issue of CDC's journal, "Emerging Infectious Diseases," the 3,642 cases of CJD reported through CDC's mortality system during the 16 year period, 1979 through 1994, demonstrated relatively stable total annual rates of this disease in the United States. These relatively stable annual CJD death rates of about 1 case per million population and existing evidence that persons with CJD do not differ from control subjects in their history of receiving or donating blood support the following conclusion. Despite regular blood donations by donors who subsequently develop CJD, blood

transfusions do not appear to be amplifying CJD infections in the population.

CDC's national mortality surveillance revealed that none of the 3,642 cases of CJD were reported also to have had hemophilia, thalassemia or sickle cell disease, diseases with increased exposure to blood or blood products. Because many of the patients with these diseases are exposed to blood products at a very early age, it is also noteworthy that no CJD cases were reported in persons 5 to 19 years of age in the United States during the 16 year period.

Clotting factor concentrates, used by hemophilia patients to control bleeding, are commonly derived from the plasma of between 4,000 and 30,000 donors. Since regular recipients of such concentrates can be expected by chance alone to have had exposure to CJD donors through these treatments, hemophilia patients constitute an important sentinel group for assessing the possible infectivity of a blood product from such donors. Thus, in addition to general CJD surveillance through mortality data, CDC has sought cases of CJD specifically among persons with hemophilia.

About 13,000 of the estimated 17,000 hemophilia population in the United States are cared for in hemophilia treatment centers. Despite the increased publicity about CJD in this hemophilia

community since late 1994, no case of CJD in a hemophilia patient has been confirmed to date. In addition to alerting over 120 US hemophilia treatment centers in September 1995 about CJD surveillance, CDC has continued to make follow-up inquiries quarterly to the largest of these centers where the majority of the active hemophilia patients are enrolled. CDC has also received brain tissue from 25 deceased hemophilia patients for neuropathologic study to help further assess the possible presence of CJD in hemophilia patients. As of January 15, 1997, the neuropathologic study results on 19 were complete; none had evidence of CJD.

In 1995, CDC and the American Red Cross initiated a long term followup study of recipients of blood components derived from CJD donors who may be reported either to the American Red Cross or to another blood center that might wish to participate. This ongoing investigation has determined the vital status, and if deceased, whether CJD was the cause of death, in at least 130 recipients of blood components from 10 CJD donors. At last report, none of these recipients had died of CJD. Twenty-three had lived 5 or more years after their receipt of a blood component from a CJD donor, including 4 who had lived 13, 14, 16 and 25 years afterwards.

In conclusion, despite some laboratory, experimental evidence suggesting a potential for bloodborne transmission of CJD, the

accumulating epidemiologic data have strengthened CDC's original conclusion that the risk, if any for transmission of CJD by blood products is extremely small and theoretical. Periodic reevaluations of accumulating data will undoubtedly provide a stronger basis for modifying, as appropriate, public health policies on CJD and blood safety in the future.

CONCLUSION

In May 1996, the Director of CDC testified before this subcommittee that history tells us that infectious diseases will remain important evolving, complex public health problems. The two public health issues concerning CJD that I have addressed today illustrate this point. To meet these complex challenges, we must strengthen our capacity to address the threat of emerging infectious diseases. Investments in surveillance and response, laboratory research and training, and epidemiologic investigations will ensure that we are better prepared to respond and lessen the impact of infectious disease threats. In addition, they underscore the importance of CDC maintaining a strong capacity to help assess, respond, and lessen the impact of infectious disease threats.

Thank you for the opportunity to discuss these issues concerning CJD and how our CJD surveillance data help in assessing risk. I

will be happy to answer questions you or other member of the subcommittee may have.

Mr. SHAYS. Thank you, Dr. Schonberger.

Dr. Gibbs.

Mr. GIBBS. Thank you. I would like to thank the subcommittee for inviting me to participate in the hearing. My name is Clarence Joseph Gibbs, Jr. I am a Ph.D., and I received my undergraduate and graduate degrees from the Catholic University of America here in Washington, DC. For more than 30 years I have served as a research scientist and currently as the Acting Chief of the Laboratory of Central Nervous System Studies, Division of Intramural Research, National Institute of Neurological Disorders and Stroke at the National Institutes of Health.

I also hold appointments as teaching and research Associate Professor, Department of Neurology and Department of Pathobiology of the Johns Hopkins University Medical Center, Baltimore.

I also serve on numerous interagency task forces, including the Public Health Service Interagency Coordinating Committee on Human Growth Hormone and Creutzfeldt-Jakob disease, Interagency Committee on Bovine Spongiform Encephalopathy and the Interagency Animal Model Committee.

I also serve as senior scientist and consultant chairman on the transmissible spongiform encephalopathies, to the Division on Emerging Diseases of the World Health Organization in Geneva and to the Division of Neurosciences of the Pan American Health Organization.

Today, I will provide a brief overview of the transmissible spongiform encephalopathies and discuss the implications for human use of animal products and the safety of the blood supply.

Mr. Chairman, as I prepared this testimony which addresses rather recent health concerns, I was struck by the fact that much of our understanding of these topics stems from a study of child growth and disease patterns in primitive cultures, first initiated in our Neurology Institute by Carleton Gajdusek in 1959.

Forty years ago the study of the spreading epidemic of kuru, a fatal neurological disease in children and adults in the remote highland interior of New Guinea, led to the first recognition and demonstration in our laboratory of slow virus infections of man. Kuru occurred in Stone Age cultures where it was spread by contamination of infants, children, and adult females with brain tissue in a mourning ritual of cannibalistic respect for the dead. Discovery of such slow infections led our laboratory to demonstrate that Creutzfeldt-Jakob disease and Gerstmann-Straussler-Scheinker syndrome were caused by infectious agents that were related to the agent causing scrapie in sheep and goats. The kuru discovery also led us to recognize that fatal subacute sclerosing panencephalitis is a delayed and slow measles virus infection; that transverse myelitis and adult T-cell leukemia are the result of human lymphotropic virus type-I human retrovirus infection; and that AIDS is a slow infection with the HIV retrovirus.

Our kuru study led to the identification of a new group of subviral pathogens in which the infectious agent is not a nucleic acid, but which are beta-pleated proteins or amyloids often called prions. The diseases caused by these agents are characterized by brain tissue giving a "spongy" appearance upon examination under the microscope, hence the term spongiform encephalopathy. In more mod-

ern societies, the medically induced spread of Creutzfeldt-Jakob disease has been shown to result from contaminated human growth hormone, dura mater grafts, corneal transplants and brain electrodes which are viewed as the result of intended beneficial invasive procedures.

The onset of the rapidly fatal central nervous system diseases caused by these agents may occur many decades after primary infection by the peripheral route. On inoculation directly into the brain or eye, incubation periods may be only 1 to 2 years.

Our recognition that the Gerstmann-Straussler-Scheinker syndrome was transmissible and thus belonged to the group of spongiform encephalopathies demonstrated for the first time that a human brain disease can arise in an autosomal dominant pattern of inheritance, but at the same time can arise through infection. This in turn led to our elucidation that familial forms of Creutzfeldt-Jakob disease and related diseases are due to mutations on the gene of the prion protein. This combination of genetic and infectious etiology had not been previously described in human medicine.

We have demonstrated infection as the etiology of five human diseases and five diseases affecting animals. These we have classified as the Transmissible Spongiform Encephalopathies, or more correctly the Transmissible Cerebral Amyloidoses. In humans they are: kuru, Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker syndrome, Fatal Familial Insomnia, and the new variant Creutzfeldt-Jakob disease first observed in Britain last year. In animals these include scrapie, transmissible mink encephalopathy, chronic wasting disease of deer and elk, and bovine spongiform encephalopathy. All are experimentally transmissible to nonhuman primates and laboratory rodents. These transmissions have permitted us to determine the pathogenesis of each of these diseases and to demonstrate their unique physical, biological and biochemical properties. As a group, their infectivity is resistant to treatment with most organic and inorganic chemicals, they are thermostable, and high levels of ionizing radiation and ultraviolet light have no effect. Moreover, we have tested literally hundreds of drugs in infected animals and a number have been administered to a few patients by non-NIH physicians without success.

The recent French report that the prion protein is not detectable in material that transmits BSE to mice does not necessarily demonstrate that the infectious agent is something other than the beta-pleated protein. The transmission of an infectious amyloid disease without detectable PrP, or prion protein, in the brain should not be surprising. The assay for prion protein is not sufficiently sensitive to detect it before infectious titers, that is, levels in the brain, reach many thousands of infectious doses per gram. In the mid 1960's, we demonstrated with our French and English collaborators that during the early incubation of the transmissible spongiform encephalopathies, when the virus titer in the brain was still very low, there were already marked functional changes, even though no pathology was yet detectable, even by electron microscopy. A month or two later, polynucleation of neurons appeared in spider monkeys, incubating kuru, and somewhat later, microvacuolation and membrane changes visible only by electron microscopy. This pre-

ceded the first appearance of astrogliosis and spongiform change. It was only much later that the classical scrapie-TSE pathology appeared with virus titers in brain of 10 to the minus 5 or higher. Thus, it is clear that early replication to only low infectivity titer, far below that necessary to detect prion protein biochemically or immunologically, can already lead to disease, including the cardinal electroencephalographic change signs of extensive hypsarhythmia of the Lennox-Gastaut syndrome in rhesus monkeys. It is no surprise that on further passage, especially into a different host, prion protein appears at detectable levels. Thus, in my view, the recent French work reported in *Science* does not indicate that an infectious amyloid is not responsible for the disease. Instead, it further confirms that such a nucleating protein is present, since prion protein appears on passage into a host producing high titer of the nucleating agent.

In Fatal Familial Insomnia, many patients have no detectable prion protein, and presumably very low titer infectious amyloid. Yet this early nucleation is sufficient to cause progressive fatal neurophysiological derangement. Dr. Brown in our laboratory has demonstrated that there is considerable variability in the presence of prion protein in different brain areas in different cases of FFI and CJD; in certain areas often none is found. Variation in the concentration and distribution of the infectious protein has also been noted in bovine spongiform encephalopathy in infected cattle brain.

The committee has asked that I discuss the differences between the transmissible spongiform encephalopathies in human immunodeficiency virus, another slow infectious agent. As noted earlier, the so-called conventional viruses, including retroviruses such as HIV, do cause slow infection. The differences, however, are that unlike the spongiform encephalopathies, conventional viruses contain either DNA or RNA, induce specific antibodies, are inactivated by most chemicals, heat and radiation, and can be identified by electron microscopy and immynological techniques.

Early in the course of our studies we sought to determine the mode of transmission in these diseases, particularly in Creutzfeldt-Jakob disease, since 90 percent of the cases occur sporadically at the rate of one to two deaths per million population wherever you look for it. We had ample evidence that in kuru there is no vertical transmission and no evidence of infectivity in blood or breast milk. The same can be said about our inability to detect infectivity in donor units of Creutzfeldt-Jakob disease human whole blood transfused to chimpanzees or packed lymphocytes from patients inoculated into small monkeys more than 20 years ago. In spite of these early negative studies which are still in progress, concern about the possibility of transmitting Creutzfeldt-Jakob disease through blood or blood products has arisen in recent years as increasing numbers of blood donors who later died from CJD have been identified. Substantial evidence from experimentally infected animals, and fragmentary evidence from humans with CJD, indicates that blood, and particularly white blood cells, may sometimes contain low levels of the infectious agents. We are conducting a study in collaboration with the National Heart, Lung and Blood Institute, Food and Drug Administration, the American Red Cross, and the Communicable Disease Center to address two specific questions.

First, we seek to determine the distribution of infectivity in components and plasma derivatives of normal human blood to which had been added a large amount of the infectious agent; that is, to see whether any blood component or plasma derivative might be free of infectivity in spite of an unrealistically large infectious input. For this study we added a suspension of high titer hamster scrapie brain cells to normal whole blood and will assay them for infectivity. Second, we will determine the distribution of infectivity, if present at all, in components and derivatives in an experimental model characterized by a low blood level of circulating pathogen. For this study, we chose to analyze blood from terminally ill mice that had been inoculated with a mouse-adapted strain of Creutzfeldt-Jakob disease in order to look for infectivity.

In addition, we have initiated attempts to isolate the infectious agent from the blood and blood products of humans with clinically evident CJD, as well as mutation-positive but still healthy members of CJD families to examine the infectious status of blood during the preclinical phase of disease. These specimens will be inoculated in parallel into two types of assay animals: squirrel monkeys: known susceptibility, but expensive, and with an extended period of observations; and transgenic mice carrying a human prion protein gene insert: limited knowledge about susceptibility, but less expensive, with a period of observation of less than 2 years.

It is important to note that there has never been a recorded case of CJD in a hemophiliac patient.

In view of the fact that none of the transmissible spongiform encephalopathies have proven susceptible to treatment, there is understandable concern about human exposure to food and other products from infected animals.

Since only 2 of the 6,000 patients in the world have been under 20 years of age, and none under 14 years of age, we have pointed out that the appearance at this time in Great Britain of CJD in adolescents and prepubertal children could represent a possible link with the bovine spongiform encephalopathy epidemic. This would not mean that beef or sausage produced from mixtures including viscera of slaughtered cattle animals was the cause, nor could it clearly implicate the milk and milk products.

Mr. SHAYS. I am going to ask you if you would bring your statement to a conclusion. I think you have been in this business so long that I am afraid that you can keep us here a long time.

Mr. GIBBS. I could keep you forever.

Mr. SHAYS. I know you could.

Mr. GIBBS. I don't mind talking.

Mr. SHAYS. I understand.

Mr. GIBBS. All right, I will wind it up, then, Mr. Chairman.

Mr. SHAYS. Thank you.

Mr. GIBBS. I would simply like to wind it up by saying that our current research efforts continue to focus entirely on the transmissible spongiform encephalopathies.

In addition to our overall efforts on these diseases, we are concentrating on the following areas: The studies we have proposed for blood and blood products; the isolation, purification, and characterization of the normal prion protein and the method of its conver-

sion into its pathological abnormal isoform; and the molecular biology of the spongiform encephalopathy.

And finally, Mr. Chairman, I would like to say that in the four decades that I've been working in this field, all of our work has been done in collaboration with Food and Drug Administration, Department of Agriculture, Centers for Disease Control, all the Federal agencies. But just as importantly, it has involved most of academia in the United States and, by and large, it is fully international in scope and in work.

Thank you, Mr. Chairman, for the opportunity for presenting this testimony.

[The prepared statement of Mr. Gibbs follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

Statement of

Clarence J. Gibbs, Ph.D.

Laboratory of Central Nervous System Studies

National Institute of Neurological Disorders and Stroke

National Institutes of Health

before the

Committee on Government Reform and Oversight

Subcommittee on Human Resources and Intergovernmental Relations

U.S. House of Representatives

January 29, 1997

For Release Only Upon Delivery

Mr. Chairman, I wish to thank the Subcommittee for inviting me to participate in hearings on the topic "Mad Cow Disease" and risks associated with the transmissible spongiform encephalopathies, or TSEs. My name is Clarence Joseph Gibbs, Jr. I am a Ph.D. and received my undergraduate and graduate degrees from the Catholic University of America here in Washington D.C. For more than 30 years I have served as a Research Scientist and currently as the Acting Chief of the Laboratory of Central Nervous System Studies, Division of Intramural Research, National Institute of Neurological Disorders and Stroke, National Institutes of Health. I also hold appointments as teaching and research Associate Professor, Department of Neurology and Department of Pathobiology, Johns Hopkins University Medical Center, Baltimore Maryland. I also serve on numerous interagency government task forces including the PHS Interagency Coordinating Committee on Human Growth Hormone and Creutzfeldt-Jakob Disease, Interagency Committee on Bovine Spongiform Encephalopathy and the Interagency Animal Model Committee. I also serve as senior scientist and consultant chairman on the transmissible spongiform encephalopathies, to the Division on Emerging Diseases of the World Health Organization in Geneva and to the Division of Neurosciences of the Pan American Health Organization.

Today I will provide a brief overview of the transmissible spongiform encephalopathies and discuss the implications for human use of animal products and the safety of the blood supply.

Transmissible Spongiform Encephalopathies--a New Class of Diseases

Mr. Chairman, as I prepared this testimony, which addresses rather recent health concerns, I was struck by the fact that much of our

understanding of these topics stems from a Study of Child Growth and Disease Patterns in Primitive Cultures first initiated in the Neurology Institute by Carleton Gajdusek in 1959.

Forty years ago the study of the spreading epidemic of kuru, a fatal neurological disease in children and adults in the remote highland interior of New Guinea, led to the first recognition and demonstration in our NIH laboratory of slow virus infections of man. Kuru occurred in stone age cultures where it was spread by contamination of infants, children and adult females with brain tissue in a mourning ritual of cannibalistic respect for the dead. Discovery of such slow infections led our laboratory to demonstrate that Creutzfeldt-Jakob disease (CJD) and Gerstmann-Straussler-Scheinker syndrome (GSS) were caused by infectious agents that were related to the agent causing scrapie in sheep and goats. The kuru discovery also led us to recognize that fatal subacute sclerosing panencephalitis (SSPE) is a delayed and slow measles virus infection; that transverse myelitis and adult T-cell leukemia are the result of human T-cell Lymphotropic virus type-I (HTLV-I) human retrovirus infection; and that AIDS is a slow infection with the HIV retrovirus.

Our kuru study led to the identification of a new group of subviral pathogens in which the infectious agent is not a nucleic acid, but which are beta-pleated proteins or amyloids often called prions. The diseases caused by these agents are characterized by brain tissue giving a "spongy" appearance upon examination under the microscope, hence the term "spongiform encephalopathy". In more modern societies, the medically induced spread of CJD has been shown to result from contaminated human growth hormone, dura mater, corneal transplants and

brain electrodes which are viewed as the result of intended beneficial invasive procedures.

The onset of the rapidly fatal central nervous system diseases caused by these agents may occur many decades after primary infection by the peripheral route. On inoculation directly into the brain or eye, incubation periods may be only 1 to 2 years.

Our recognition that the Gerstmann-Straussler-Scheinker syndrome was transmissible and thus belonged to the group of spongiform encephalopathies demonstrated for the first time that a human brain disease can arise as an autosomal dominant pattern of inheritance but at the same time can arise through infection. This in turn led to our elucidation that familial forms of CJD and related diseases are due to mutations on the gene of the prion protein. This combination of genetic and infectious etiology had not been previously described in human medicine.

We have demonstrated infection as the etiology of five human diseases and five diseases affecting animals. These we have classified as the Transmissible Spongiform Encephalopathies, or more correctly the Transmissible Cerebral Amyloidoses. In humans they are: kuru, Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker syndrome, Fatal Familial Insomnia, and the new variant CJD first observed in Britain last year. In animals, these include scrapie, transmissible mink encephalopathy, chronic wasting disease of deer and elk, and bovine spongiform encephalopathy (BSE). All are experimentally transmissible to nonhuman primates and laboratory rodents. These transmissions have permitted us to determine the pathogenesis of each of these diseases, and to demonstrate their unique physical, biological and biochemical

properties. As a group, their infectivity is resistant to treatment with most organic and inorganic chemicals, they are thermostable, and high levels of ionizing radiation and ultraviolet light have no effect. Moreover, we have tested literally hundreds of drugs in infected animals and a number have been administered to a few patients by non-NIH physicians without success.

The recent French report that PrP protein is not detectable in material that transmits BSE to mice does not necessarily demonstrate that the infectious agent is something other than the beta-pleated protein. The transmission of an infectious amyloid disease without detectable PrP in the brain should not be surprising. The assay for PrP is not sufficiently sensitive to detect it before infectious titers--that is, levels in the brain--reach many thousands of infectious doses per gram. In the mid-1960s, we demonstrated with our French and English collaborators that during the early incubation of the TSEs, when the virus titer in the brain was very low, there were already marked functional changes, even though no pathology was yet detectable, even ultrastructurally. A month or two later, polynucleation of neurons appeared in spider monkeys, incubating kuru, and somewhat later, microvacuolation and membrane changes visible only by electron microscopy. This preceded the first appearance of astrogliosis and spongiform change. It was only much later that the classical scrapie-TSE pathology appeared with virus titers in brain of 10^{-5} or higher. Thus, it is clear that early replication to only low infectivity titer, far below that necessary to detect PrP biochemically or immunologically, can already lead to disease. It is no surprise that on further passage, especially into a different host, PrP appears at detectable levels. Thus, in my view, the recent French work reported in ***SCIENCE*** does not indicate that an infectious amyloid is not responsible for the disease.

Instead, it further confirms that such a nucleating protein is present, since PrP appears on passage into a host producing higher titer of the nucleating agent.

In Fatal Familial Insomnia (FFI), many patients have no detectable PrP and presumably, very low titer infectious amyloid. Yet, this early nucleation is sufficient to cause progressive fatal neurophysiological derangement. Dr. Brown in our laboratory has demonstrated that there is considerable variability in the presence of PrP in different brain areas in different cases of FFI and CJD; in certain areas often none is found. Variation in the concentration and distribution of the infectious protein has also been noted in BSE infected cattle brains.

The committee has asked that I discuss the differences between the TSEs and Human Immunodeficiency Virus (HIV), another slow infectious agent. As noted earlier, the so-called "conventional viruses," including retroviruses such as HIV, do cause slow infections. The differences, however, are that unlike the spongiform encephalopathies, conventional viruses contain either DNA or RNA, induce specific antibodies, are inactivated by most chemicals, heat, and radiation, and can be identified by electron microscopy and immunological techniques.

Creutzfeldt-Jakob Disease and the Blood Supply

Early in the course of our studies we sought to determine the mode of transmission in these diseases, particularly in Creutzfeldt-Jakob disease, since 90% of the cases occur sporadically at the rate of 1-2 deaths per million population wherever you look for it. We had ample evidence that in kuru there was no vertical transmission and no evidence of infectivity in blood or breast milk. The same can be said about our

inability to detect infectivity in donor units of CJD human whole blood transfused to chimpanzees or packed lymphocytes to small monkeys more than 20 years ago. In spite of these early negative studies which are still in progress, concern about the possibility of transmitting Creutzfeldt-Jakob disease (CJD) through blood or blood products has arisen in recent years as increasing numbers of blood donors who later died from CJD have been identified. Substantial evidence from experimentally infected animals, and fragmentary evidence from humans with CJD, indicates that blood - and particularly white blood cells - may sometimes contain low levels of the infectious agent. We are conducting a study in collaboration with NHLBI, FDA, and the American Red Cross to address two specific questions.

First, we seek to determine the distribution of infectivity in components and plasma derivatives of normal human blood to which had been added a large amount of the infectious agent, *i.e.* to see whether any blood component or plasma derivative might be free of infectivity in spite of an unrealistically large infectious input. For this study, we added a suspension of high titer hamster scrapie 263-K strain-infected brain cells to normal whole blood and will assay them for infectivity. Second, we will determine the distribution of infectivity (if present at all) in components and derivatives in an experimental model characterized by a low blood level of circulating pathogen, *i.e.* a condition probably analogous to the situation in humans with CJD. For this study, we chose to analyze blood from terminally ill mice that had been inoculated with a mouse-adapted strain of CJD in order to look for infectivity.

In addition, we have initiated attempts to isolate the infectious agent from the blood and blood products of humans with clinically

evident CJD, as well as mutation-positive but still healthy members of CJD families (to examine the infectious status of blood during the pre-clinical phase of disease). These specimens will be inoculated in parallel into two types of assay animals: squirrel monkeys (known susceptibility, but expensive, with an extended period of observations), and transgenic mice carrying a human PrP gene insert (limited knowledge about susceptibility, but less expensive, with a period of observation of less than 2 years). It is important to note that there has never been a recorded case of CJD in a hemophiliac patient.

Animal TSEs and Human Health

In view of the fact that none of the TSEs have proven susceptible to treatment, there is understandable concern about human exposure to food and other products from infected animals. Since only two of the 6000 diagnosed CJD patients in the world have been under 20 years of age, and none under 14 years of age, we have pointed out that the appearance at this time in Great Britain of CJD in adolescents and prepubertal children could represent a link with the bovine spongiform encephalopathy (BSE) epidemic. This would not mean that beef or sausage produced from mixtures including viscera of slaughtered cattle was the cause, nor could it clearly implicate the milk and milk-products. All would remain possibilities. However, it is important to note that no infectivity has been detected in the breast milk of nursing mothers dying with kuru or in milk or mammary gland tissues of cattle with BSE.

Pigs held for eight years after intercerebral inoculation with BSE develop a transmissible spongiform encephalopathy. In contrast, pigs inoculated with kuru or Creutzfeldt-Jakob disease failed to develop disease or have detectable infectious protein in their brains. We do

not yet know whether the BSE agent takes orally in pigs. Contaminated bone meal was fed to pigs. Thus, meat and other tissues of the pig might harbor low-level infectivity at the time of slaughter at an early age.

We also do not know whether the agent replicates in chicken or other poultry. BSE-contaminated bone meal was fed to chickens. Poultry would be expected to shed massive quantities of the infectious amyloid in their feces. Chicken manure is widely used as fertilizer on vegetable crops. This means that vegetarians might be at risk. It is best to admit our ignorance rather than to imply that we have information about this.

Any protein chemist would assume that the extremely hydrophobic scrapie agent would enter the hydrophobic lard or tallow in a rendering plant and would appear in very low titer in the hydrophilic bone meal. Experiments to date ruling out contamination of lard are certainly not adequate. I do not know what effect the presence in fat would have on absorption of the infectious protein or its processing in a cell, and thus the virus titer. I do not know how to titrate a virus in butter.

Is scrapie pathogenic for man? We do not know and have no ethical way of determining whether scrapie is pathogenic for man. From the very beginning of our studies and in collaboration with colleagues at the US Department of Agriculture we have tried to demonstrate a causal relationship between the human and animal spongiform encephalopathies without success--but our efforts continue. The epidemiology of CJD in the United Kingdom will tell us in due course whether BSE has spread to man. If it has, we should, as in the kuru epidemic, expect to find cases in children.

As to the possibility that BSE may become endemic, I have proposed the following hypothesis. Since we accept that sporadic CJD is the result of a configurational change in a normal protein that occurs at the rate of 1-2 cases per million population per year, and since normal prion protein has been detected in all mammalian species thus far tested, as well as in salmon fish and Drosophila, then the rare occurrence of spongiform encephalopathy may certainly take place but remain undetected due to its rare occurrence in nature. It is because of this possibility that I fully endorse the Food and Drug Administration's proposed regulation on banning the feeding of meat and bone meal to ruminants derived from the rendering of ruminants. If we have learned one important lesson from the epidemic of "Mad Cow Disease" in England it is the danger associated with ruminant-to-ruminant dietary supplements from indiscriminate rendering.

Current and Future Research Directions

Mr. Chairman, our current research efforts continue to focus entirely on the transmissible spongiform encephalopathies. In addition to our overall efforts on these diseases we are concentrating on the following areas which we believe to be the most important:

~ The studies we have already initiated on blood and blood products.

~ The isolation, purification and characterization of the normal prion protein and the method of its conversion into its pathological abnormal isoform.

- The molecular biology and molecular genetics of the transmissible spongiform encephalopathies and their genetic linkage.

- The further development of simple and reliable ante-mortem diagnostic tests for the human and animal diseases. In this regard we have recently published in the *NEW ENGLAND JOURNAL OF MEDICINE* the details on our development of a test for the detection of a marker protein in the cerebrospinal fluid of humans with spongiform encephalopathies that is 96% sensitive and 99% specific and from sheep with natural scrapie and cattle experimentally infected with scrapie and mink encephalopathy. We have expanded these studies looking for markers in other bodily tissues and fluids.

In conclusion, Mr. Chairman, I wish to point out to you and the Committee that the studies our laboratory has conducted over more than three and one-half decades have been collaborative studies not only on an inter-agency basis but on a national and international basis throughout the world.

Mr. Chairman, this concludes my prepared statement. I would be happy to answer any questions you or the Subcommittee may have.

Mr. SHAYS. I thank the gentleman. It has been very important for us to hear your testimony. I am sorry we have had a little bit of distraction.

I am going to invite any of the guests that are sitting up in the front to move away from the table. Thank you. And again I apologize to those of you who have been trying to have a place to sit, and we will try to make sure we deal with that next time.

At this time I would ask Mr. Towns. You have the floor, Mr. Towns.

Mr. TOWNS. Thank you very much, Mr. Chairman.

Let me just sort of indicate that we do not want to frighten anyone, as was already indicated, but we want to make certain that everyone is safe.

Dr. Friedman, what steps has the FDA taken to issue a warning to hunters and other communities like Indian reservations where there is a high consumption of venison and other wild game that could be actually infected by BSE?

Dr. FRIEDMAN. Our Center for Food Safety has been in touch with individuals associated with State wildlife commissions, especially for the State of Colorado and for the Department of Wildlife Management for Wyoming.

There has been quite an active program on the State level to do two things. One is to better assess the incidence of these chronic degenerative diseases in the deer and elk that are being hunted and to find out as much as they can about the incidence of these infections in those populations.

A second effort that's been carried out at the State level by these individuals and by others has been to educate the hunter population to look out for animals acting unusually, to submit specimens from those animals that are killed for those specimens then to be looked at to see if the disease exists, and then to warn those hunters not to consume meat from those animals until such time as they've been tested or, if there is any doubt, to be extra safe and to not do it at all.

We recognize that assessing the wildlife population is a very difficult thing. We know of these two areas where this chronic disease does exist, and we feel that this is a very good start toward educating those populations.

Mr. TOWNS. Do you feel there are other things that should be done?

Dr. FRIEDMAN. I think we're still at the point of gaining information about how widespread the penetrance is of this abnormality in the deer and elk populations in the United States.

I think that educating the community of hunters to look out for animals acting unusually is a prudent thing to do. I need more information, and we're in the process of trying to gather that information before promulgating other steps, but I think this is something we're going to pay attention to for the future.

Mr. TOWNS. Thank you.

Let me raise another issue. Is there anything to be worried about in terms of cosmetics or even dietary supplements as well? Should we have any concerns?

Dr. FRIEDMAN. I think that the—I'd give you the following answer. The short answer is, I don't believe so. Now let me document

why that is. It is not a simple assertion, and it is not one made without careful consideration.

In a situation where you don't have all the scientific information, and we do not, we must be mindful and open minded of new information as it emerges. The second thing is that we should have a threshold which is relatively low to protect the American public.

We know that for the last several years there has been an import alert partially done by the Food and Drug Administration. There's been an import prohibition from the U.S. Department of Agriculture for those products coming into the United States from BSE animals and BSE countries.

We have more recently received information from the European Community that there is an absolute prohibition on using BSE animal parts in cosmetics not only for use within the European Community but it's also a prohibition for export to other places, like the United States we must presume.

Therefore, as we look at the wide variety of products that are used in cosmetics, we see that the vast majority of those are coming from non-BSE countries and that, with new rules being promulgated by the European Community, we're very comfortable with products made in the United States. We know there is no BSE, we know that those are—from U.S. animals do offer the American public the confidence that they need, and we see efforts being made by foreign governments to try to do that as well.

Mr. TOWNS. Thank you.

Is there any evidence that blood products have been linked to CJD?

Dr. FRIEDMAN. I'd be happy to let the Centers for Disease Control answer that as well. But our review of this says that we have not been able to demonstrate convincingly any case of blood-borne transmission of CJD.

Dr. SCHONBERGER. The evidence for some concern at all comes from laboratory and experimental studies. There have been four different reports in the literature where the researchers have said that they've been able to isolate or to show infectivity of blood in a sick CJD patient.

Of course we're worried in the blood risks area about what happens before the donor with CJD gets sick because that's when this person donates the blood.

In that area, there's some animal model studies that have demonstrated that in those animal models—and we're talking about rodents now who have been injected with a high dose of the infectious material. In those rodents, indeed we can detect infectivity in the blood throughout much of the incubation period. So that's the basis for the theoretical risk concern.

Now, at CDC we're interested in looking at what does this mean in terms of the human risk, and in that area we have not been able to demonstrate or find any evidence, any convincing case resulting from exposure to blood or blood products, including hemophilia patients, who are known, because of the clotting factor that they receive, to be statistically exposed to a CJD donor at some point because of the 10,000 to 30,000 different donors that contribute to the concentrate that they receive.

And if the person who is a hemophiliac gets treated as a youngster for many years, somewhere along the line one of those donors is going to have been incubating CJD. And yet we still don't have an increased risk in the hemophilia population. We're getting to the point now where you'd almost expect a case by chance alone given the size of their population, and we can't even find that case.

So the bottom line from our perspective is that it is a theoretical risk, for the reasons that I've cited, but it is not as yet really a real risk, and so our control measures need to take that into consideration.

And what we want to make sure that we do—and we are talking here about balance—is that we don't institute control measures that are more risky than the risk itself of the disease from the product that we're talking about; and that's the tricky balance.

In this area, the newspapers and other public media can be helpful to us because they need to educate the recipients of blood products to know that there is this theoretical risk, OK, but it's not a real risk, not something to be scared about at this point. There is nothing there now to indicate the real risk.

Mr. TOWNS. Dr. Friedman, let me ask you this, then: What are you doing to monitor blood products?

Dr. FRIEDMAN. This is a joint effort between the Centers for Disease Control, ourselves, and organizations like the American Red Cross.

The monitoring takes place in a couple of different ways. The first is to try to identify those donors who, unbeknownst to themselves, already have CJD and may show the clinical symptoms at some later date.

We need to identify those individuals, identify individuals who are at high risk of having the disease for familial reasons, and then to segregate off their blood products to make decisions. That's one sort of observation.

A second set of observations are for those individuals who receive blood products from a CJD donor who didn't know he or she had CJD at the time they made the donation, and then to carefully evaluate those individuals to look for the sort of long-term findings that we're talking about.

Clearly there is a theoretical risk, but we know that this is not a highly infectious situation. It has been estimated that each day, despite the very best efforts of the blood programs and in our own efforts and other efforts at the State level, despite those best efforts, we know that there are CJD individuals donating blood unbeknownst to themselves and unbeknownst to the blood bank, and yet we're not seeing a rise and we're not seeing cases of CJD resulting from that, so that we know that the risk may be very, very small.

That doesn't make us comfortable. It only makes us more vigilant.

Mr. TOWNS. It didn't make me more comfortable either.

Dr. FRIEDMAN. No. And that's absolutely correct, sir.

Mr. TOWNS. Thank you, Mr. Chairman.

Mr. SHAYS. Thank you, Mr. Towns.

The gentleman has the floor.

Mr. PAPPAS. Could any of the panelists tell me or tell the rest of us, as well, have there been any other recorded incidents of any other species in any other country that may suffer from BSE or scrapie or any other similar type of disorder?

Dr. DETWILER. I can address the animal area. These other spongiform encephalopathies in animals that have been detected are scrapie in sheep. Most of the world actually is thought to have countries where scrapie is endemic.

Probably the two that might be recognized as scrapie free throughout the world—and that's not by everyone but commonly—are New Zealand and Australia for scrapie.

Another disease called transmissible mink encephalopathy that's been diagnosed in ranch-raised minks, it has been diagnosed in the United States. The last case was in 1985. Prior to that, we had cases in 1947 and a few in early 1960's. TME, or mink encephalopathy, has also been diagnosed in Canada, Russia, Finland, and Germany. Chronic Wasting Disease, that's of the captive mule, deer, and elk in the United States; there's been a spongiform encephalopathy diagnosed in cats, both domestic and large cats. That's been in the domestic cats in the United Kingdom; 75 cases, 1 in Norway, 1 in Lichtenstein, that's been associated with feed as well, and in exotic ruminants in zoos also associated with feed in the United Kingdom.

And when I say the exotics, I mean kudu or the gemsboks, things that you normally see on the plains, in zoos.

So that's the animal spongiform encephalopathies.

Mr. PAPPAS. And is there any reason to believe that these have any reason to spread? I mean, many of those instances you've spoken about were decades ago, so it sounds as though the incidents come less and less.

Dr. FRIEDMAN. If I might just offer one observation, there seems to be for many of these diseases fairly solid species barriers between one species infecting another. Herdsmen have lived with scrapie-infected sheep for hundreds of years and there hasn't been a disease easily identifiable with that.

So there has been sheep shearing and slaughtering and so forth, and even under those sort of situations we haven't seen a human disease that we can easily point to. That doesn't mean that it couldn't occur, but it means that for many of the most prevalent diseases we haven't seen that in humans.

The question of what's happening with BSE and the new variant Creutzfeldt-Jakob disease is an area of very intense investigation, as has been described.

Dr. DETWILER. One other point to make with the animal spongiform encephalopathies: There doesn't seem to be between species, like sheep and cattle, contagious spread. There's no evidence of that at all, like if you house cattle with sheep versus one sheep spread from one to the other.

Mr. PAPPAS. By each of your identifications here as to which Federal agency that you're identified with, we have the Food and Drug Administration, we have U.S. Department of Agriculture, Centers for Disease Control and Prevention, and National Institutes of Health.

Are there other Federal agencies that are involved in researching these issues?

Dr. DETWILER. The Agricultural Research Service, part of the U.S. Department of Agriculture, is extremely involved. We work with them, as does NIH and the others.

Mr. PAPPAS. Is there any—and this is not to suggest that I don't agree with the research that is ongoing, but is there any reason to believe that there is any duplication of effort by you folks?

Dr. FRIEDMAN. Do you mean in terms of research?

Mr. PAPPAS. Any of the involvement that you and your peers and colleagues in the various agencies, yes.

Mr. GIBBS. I'd like to address that. In my experience throughout the years, there has been no duplication, it has been a collaborative effort, and, by and large, it has been one agency covering one aspect, another agency covering a different aspect based on the discipline involved in that institute.

So, in fact, there's been no duplication but certainly coordination in all of our work.

Mr. PAPPAS. Would the rest of you agree with that?

Dr. DETWILER. I'd like to also address that. I serve on an ad hoc group for an agency known as Office of International Epizootics to represent the United States, and that agency also coordinates research efforts. We had a meeting in October in France to do that. And you would find that, almost worldwide, that this community of researchers does not seem to duplicate but to coordinate. And I know with ARS and efforts we've done within the Department of Agriculture, we've had even international coordination so that we don't do duplication.

Mr. PAPPAS. So even within the agencies of the U.S. Government, is there a similar body where there is a coordinating body that periodically meets or consults with one another to ensure that this concern for duplication doesn't take place?

Dr. FRIEDMAN. Let me try and address a partial answer to that, and then I certainly would welcome other comments as well.

If you look at this in several segments, there is a mosaic of regulatory activities depending upon the responsibilities of each of the relevant areas. The U.S. Department of Agriculture has a defined set of responsibilities, and to the extent that they integrate that with the Food and Drug Administration, then our concerns about animals and ultimately their concern about people are intermeshed. And so you have to look at this as a mosaic not just at the Federal level but, I stress, at the State and other levels as well.

We couldn't function adequately without the scientific input from CDC and from NIH and from academic centers and from private scientists as well. And the reason for that is that at a time when we have incomplete information to make the best regulatory decision, we can't be paralyzed waiting for the most complete information to come about; that wouldn't be appropriate. We must make decisions, but we must make them in the most thoughtful and most appropriate way, and that has to be driven by science.

And so, by the very needs of that, there's a huge amount of communication and sharing of information both domestically and abroad, because all these communities in some sense interact.

Dr. DETWILER. Also, Mr. Pappas, the Agriculture Research Service has a committee, the BSE Research Advisory Group, where they do coordinate such efforts in the United States, and it is not only intergovernment—NIH, Paul Brown, and Joe have been invited, as well as FDA—but we also have coordinated efforts with private labs, either university labs or private, like the Basic Institute for Research in Staten Island, University of Wisconsin, Stan Prusner's lab in California, Rocky Mountain Laboratory, etc.

They recently sponsored a meeting in Ames, IA, in June to again have some papers presented as well as to meet after the meeting and to discuss further research efforts.

Mr. PAPPAS. So is it safe to say this is my last question. Is it safe to say that there is no agency that is, quote/unquote, the lead agency, or is that not correct?

Dr. FRIEDMAN. I think a more proper way to say it is that each of the agencies has a field of responsibility for which they are primarily responsible but that none of the agencies acts alone.

Dr. SCHONBERGER. For example, when the problem of CJD after receipt of human growth hormone occurred, the agencies met; and, basically, CDC wrote a protocol—an epidemiologic protocol for followup of this group of patients. And we've published on that risk. We've had 16 cases of CJD in a group of about 8,000 human growth hormone recipients.

Now, NIH tests the lots for infectivity, and they've reported, in the New England Journal of Medicine, some of the results that they have had from that type of study. So it is a collaborative effort.

Our work with the American Red Cross on following known recipients of CJD donor blood was in part a result of discussions that went on between FDA and CDC on the type of new information that would be useful and helpful in this area.

Mr. GIBBS. May I comment?

Mr. SHAYS. Sure. And then I'll call on Mr. Waxman.

Mr. GIBBS. Yes. In regard to this, I would like you to envision what it means for scientists to get together to discuss, to bare their knuckles about their work and their findings, and then to walk out of that room, each knowing he is going to do his thing or she is going to do her thing, but it is a coordinated effort.

In that regard, I would like to submit these for the record, Mr. Chairman.

Mr. SHAYS. Sure.

Mr. GIBBS. The seven different international workshops on bovine spongiform encephalopathy. Out of that has grown most of the research that has been conducted in this country and a fair amount of what's been conducted in the European Community.

So it is a sharing of information, with the work being done in the collaborative fashion that there is no duplication; rather, there is complementation.

Mr. PAPPAS. Thank you, Mr. Chairman.

Mr. SHAYS. Mr. Waxman, you have the floor.

Mr. WAXMAN. Thank you, Mr. Chairman.

I want to commend the four of you for your testimony. I think you have done an excellent job not only in your presentation to us but dealing with this problem that may or may not be a big one

in this country but we have seen to be quite horrible in Great Britain.

And people say they don't like government. But when there is a problem like this one, we sure want government to be involved and we want the research to be done, we want the regulatory tools to be exercised, because we want the public to be protected.

As I understand, what we know about this disease, we know that if cows eat parts from other cows, that there is a danger that they may get what is called mad cow disease. And so, therefore, you have acted to stop the importation of any feed or cows from any other country where there might be a problem. Is that right?

Dr. FRIEDMAN. Correct.

Mr. WAXMAN. And the second area where there is a potential would be if our cows would ingest some feed or some dietary supplement that had animal parts in it. And as I understand, what FDA is proposing is to make sure that animal feed will not have other animal parts in it.

Is that a fair statement, Dr. Friedman?

Dr. FRIEDMAN. Yes. The danger is that one cow in the United States could spontaneously develop this disease, and if we render that cow's part in other cow feed, you would amplify the infection in a silent way until it was very large. That apparently is what happened in the United Kingdom.

By making sure that those ruminant sheep and cows don't get recycled into ruminant feed even if one cow in the United States were to have spontaneously BSE, even if it occurred genetically by accident, it would be a dead end; that cow would not be recycled into other cows; and so the chance of and epidemic occurring is vanishingly small at that point.

Mr. WAXMAN. So we seem to know if it is a cow eating cow parts, there is a danger, and Dr. Gibbs told us about cannibals eating the brains of other people, and that was a way of transmitting the disease from person to person.

Dr. FRIEDMAN. Yes.

Mr. WAXMAN. Do we feel that we know that people can get this disease, the human version of it, by eating beef?

Mr. GIBBS. There is no direct——

Dr. FRIEDMAN. We're all anxious to answer.

Mr. GIBBS. In specifically answering your question, there is no definitive proof that a human being has become infected with any of the diseases from any animal affected with those diseases.

Mr. WAXMAN. So we want to close off the areas we know are either a real danger or potential danger. You want to act reasonably and prudently, and we want to know all the scientific information. But people shouldn't fear eating a hamburger; people shouldn't fear a danger in the blood supply; and people shouldn't fear that if they need a dietary supplement that has animal parts in it, that it is diseased, from what we know at this point. There's a theoretical danger, but we don't know of any great danger that people, if they are hearing about this hearing, getting up in the middle of the night and worrying about it?

Dr. FRIEDMAN. That's correct.

Mr. WAXMAN. Now let me just followup by saying you don't have complete science and these things evolve. So if you found out there

was a danger, we want to be sure that you have the tools to act and maybe act quickly even if you don't have all the information.

For example, you already are acting to stop animal parts in feed that animals will ingest, but what if there are animal parts in a product that humans would ingest? We have no reason to think there is a danger right now.

But if you found out there was a danger, Dr. Friedman, since the FDA has regulatory control over food supply which would include dietary supplements, many of which have animal parts in them, what legal authority do you have to act, and maybe quickly, without all the full knowledge about the issue, so that we won't have to wait until there is a horror story before action is taken?

Dr. FRIEDMAN. With your indulgence I'll answer in three different ways, that question, if I may.

The first is that, as a matter of fact, it is not a theoretical set of actions that we've taken, but there was a time, I believe in 1992, when an individual was diagnosed, a human was diagnosed with CJD. That individual was taking a dietary supplement, and we went to investigate to see whether that dietary supplement, which had animal parts in it, came from a country which had BSE or we have reason to be concerned.

In fact, we are prepared. We have acted in that capacity and would be ready to do so again in the future.

The second point that I would like to make is that in 1992 and again in 1994, I believe, we contacted the manufacturer of the dietary supplement to alert them to potential concerns about this matter, granted that we don't have all the scientific information, but informing them that selecting products from countries known to be free of BSE was the prudent and appropriate thing to do, keeping records and carefully tracking where materials came from was the appropriate thing to do. And we continue that dialog.

The third is, as you've pointed out, we do have some regulatory powers in this regard, and where we are, were we to find material being imported that had—was dangerous, we certainly would act to do something about that.

Mr. WAXMAN. Let me stop you right there and ask you this question, because we're going to be looking at FDA reform in this Congress, and if we're going to reform FDA, we want to be sure we're reforming it to be sure that we have an FDA to protect the public.

If you have a danger from animal parts in animal feed, you're able to tell the manufacturer, from what I heard you say in your testimony, "Stop using animal parts until you can show that it is safe."

If it came to a human supplement, dietary supplement, and it had animal parts in it, as I read the law, based on the act that we've just adopted, you have the burden to show that it is unsafe, that it shows a significant or unreasonable risk of illness or injury, and it is not the manufacturer's burden but it is yours.

You would have to then go in and be able to make this case before you can act?

Dr. FRIEDMAN. That is correct. And what we have asked, and the verb here is important, the dietary supplement manufacturers to do is to restrict their access to BSE-free countries.

Our ability to demand that or to require that is not existent now. And so this was your urging, this was—we importune them based upon the quality of the science.

Mr. WAXMAN. But you can't enforce it?

Dr. FRIEDMAN. We can't demand that. I may not be picking the word exactly right.

Mr. WAXMAN. Well, you can write them a letter saying, "Don't use imported animal parts, and keep track of the animal parts you use so we can monitor it." But if they don't want to bother to do it, there's no way you can go in there and force them to do it.

Dr. FRIEDMAN. I believe that is correct. But not having the counsel here who is the most expert in that, I would defer to that individual.

Mr. WAXMAN. Let me just say that what I'm trying to do is, as we deal with these laws elsewhere——

Dr. FRIEDMAN. Yes.

Mr. WAXMAN [continuing]. Make sure you have the ability to act when it is appropriate and needed, and not have such a high threshold before you can take any action that it may well be too late by the time you do act.

And I think we maybe went too far in the law, saying that you have to prove a significant or unnecessary risk before anything can be done. It is a higher standard than what you have to meet to act to stop animals from being exposed to animal parts.

Dr. FRIEDMAN. That's absolutely correct, sir. If I may mention one other thing, though, and that's to reiterate the point that we made earlier, which is that Great Britain has voluntarily and the European Community has enforced that animal parts from Great Britain will not be exported.

So that, that is the highest risk country, and we have two means, not ever—not just at our own borders, where we have, USDA and FDA have various prohibitions in place, but also at their own borders not to export it.

Mr. WAXMAN. Well, you've made a good point that we have to keep in mind. You are acting appropriately given the kinds of dangers we know about. I think the American public should be proud of the work that all of you are doing, and feel comfortable that this is not a risky issue right now, and all the other risks are theoretical, and you're on top of it.

What I want to explore with you in the time I have available is, as we look at other committees that have legislative jurisdiction, when you have not the complete information but enough to cause you concern as information evolves, I just want to be sure that we don't weaken the FDA by making the laws so tough that you cannot act as conscientiously and appropriately as you all have seemed to be doing in your respective agencies to date.

Dr. FRIEDMAN. Thank you.

Dr. DETWILER. I just wanted to respond that USDA's prohibitions would actually prohibit organs and tissues from ruminants to come in, which then in turn would not allow them for dietary supplementation.

Mr. WAXMAN. Of course, the danger would be if it is local, if you have some domestic animal that develops——

Dr. FRIEDMAN. Right.

Dr. DETWILER. Right, but you mentioned about import.

Mr. SHAYS. I'd like to affirm what Mr. Waxman said in terms of our sense of your contribution, both in your work and also now before this committee. We're very pleased that all four of you agreed to come.

And the purpose of this hearing was really to followup on the hearing we had in May. We knew that FDA in particular and USDA were focused on this issue, and we're determined to come out with some rulemaking. And we're happy to hear what that is and we're happy to get a sense of its impact.

Dr. Detwiler, when you mentioned New Zealand and Australia, I was surprised that you said that they had basically a tremendously good track record, given that they have such a large sheep population; and I thought you maybe could explain to me why. I was thinking in one sense that they might have a more difficult time, given they have such a large population.

Dr. DETWILER. I think being island countries helps some whenever you're talking disease risk. But again, scrapie, it is hard to assess in any of these diseases risk of freedom of a disease, because when you do actual prevalence or incidents in a country, you should be able to survey your whole population with some type of test and ascertain which animals have the disease and which don't.

Up to this time we can only really confirm the animals that show clinical evidence of the disease, so you can't do the systematic approach to those that might be infected with the agent. There seems to be no evidence, and it's based upon animals that they sell out of the country, surveillance that they've done within the country, and the fact that their quarantines have taken place on an island. They have imported animals in that have subsequently come down with scrapie, but they have been before they were introduced into their national flock. This was back in the fifties.

Mr. SHAYS. And they've been ruminant-to-ruminant feeding?

Dr. DETWILER. They have been talking about proposing to do that. I don't know if that's under way. I can find out for you.

Mr. SHAYS. OK. Is it possible that—I guess this is for you, Dr. Schonberger. Is it possible that CJD is under-reported because it gets disguised as other diseases, like Alzheimer's in particular?

Dr. SCHONBERGER. Right. There actually have been some studies of Alzheimer's disease in looking for the frequency of CJD mixed into the Alzheimer's diagnosis, and it's extremely low, actually, in the Alzheimer disease category.

The answer to your question is yes, there is some under-reporting. As a matter of fact, in the active surveillance that we instituted in the emerging infection programs last May, April and May, we were able to document about a 10 to 15 percent under-reporting based on death certificates alone and by the active surveillance areas, including, by the way, Connecticut, where we do have an emerging infection program. They contacted, as part of this surveillance, all of the neurologists and tried to identify all the cases that they could come up with.

And when you compare that with what you get through our national mortality data, you end up, as I say, with about 10 percent, 15 percent more.

I should tell you, by the way, that our surveillance for the new variant CJD, one of the characteristics of the new variant CJD is that it affects an unusually young group.

So that, as Dr. Clarence Gibbs was talking about, the median age of the new variant cases in the U.K., and we're talking about now, what is it, 14 cases there, is about 30 years old. OK, that means about they've had five cases who have died under the age of 30. We don't have those cases here.

Mr. SHAYS. One of the things that's fairly clear to me—and Dr. Detwiler, you kind of set it off in terms of the fact that you take tremendous satisfaction in the cooperation that exists within the U.S. Government, and the private sector as well, but as well within the international community—is part of that cooperation based on the fact that there is a long incubator status, and when there is an indication of TSE that real alarm bells go off because it's potentially the tip of the iceberg?

I'd open that up to anyone, but you were the one that triggered the cooperation. Maybe I should open it up to someone else, whoever would like to respond. Did you hear the question? I just want to understand——

Dr. FRIEDMAN. I think the answer is yes. But what you do is you recognize that it may be a while until you appreciate the full magnitude of an infection. And I think everyone is very chastened by what happened in the United Kingdom and how badly out of control that situation was and how difficult it was to get it under control. And therefore I think all the scientists approach this with some caution, and when they see an early case or an early indication, there is vigorous action.

Mr. GIBBS. I can only answer by stating that in the case of variant Creutzfeldt-Jakob disease in the United Kingdom, the minute the surveillance group in the U.K. detected a case, we knew about it on the telephone from them. It's that rapid communication.

Mr. SHAYS. Thank you. These are proposed regulations, and the bottom line regulation is, ruminant-to-ruminant feeding in the United States is banned.

Dr. FRIEDMAN. Yes, sir.

Mr. SHAYS. When will these take effect? And you know what I'd also like you to do, and fairly briefly, describe to me what happened after the May hearing and how that system worked to the point where on January 3d, I think you came out with your proposed rule.

Dr. FRIEDMAN. Certainly. As you recall from our previous hearing, we had the advanced notice of a proposed rule, and the number of comments that we received to that was very large, something in excess of 650; and some of these were quite lengthy and thoughtful commentaries.

We worked very hard with our colleagues and with the scientific community to try and craft the best proposal or set of proposals that we could, and in that regard we tried to balance several things. One was practicality, looking at ease, at economy, at enforceability. And always underlying this was the scientific—the imperfect scientific basis upon which we were building this proposal.

That was completed—that effort was completed in late summer, late August, and was sent forward for more full review by the de-

partment and other parts of the government, to assure that we had paid proper attention to economic issues and other regulatory concerns that are necessary, that are mandated for a rule of this magnitude. That time was longer than I would have liked in toto. Our comment period ends, I believe, in the next couple of weeks.

Mr. SHAYS. Sometime in February.

Dr. FRIEDMAN. Yes, it is early to mid-February. We're in the process of reviewing comments that we're receiving now. It is my utmost hope, and it is the commitment that I've given you personally previously, that I intend to honor, which is that I want this completed just as quickly as we possibly can.

I think there has been a value in engaging as many different people in this effort up to this point. If this is going to be truly enforceable, then having a proposal which makes sense to the largest number of people means that their participation will result in a more wholehearted way than if they didn't understand the background of this or if we didn't pay attention to practicality and economic issues that were important to them.

So what we think is ultimately what we care about is the protection of these herds and therefore the protection of the American public, and the chance of assuring that is greater by having this more broader participation at this time.

Mr. SHAYS. So when this takes effect in February, then there is no more appeal process? Would there potentially be an appeal process?

Dr. FRIEDMAN. I should really ask someone from the Center. I don't know whether there would be a further appeals process, sir.

Mr. SHAYS. Come on up, sir. Just identify yourself. You were sworn in, correct?

Dr. MITCHELL. Yes.

Mr. SHAYS. You can pick up the mike if you'd like.

Dr. MITCHELL. It's Dr. Mitchell. The comment period will close on February 18th, and that is the comment period to the proposed rule. We are receiving comments to that proposal now and there will be more coming in. We will be considering those comments and then publishing a final rule. And there will be another separate period announced in the final rule, on when the final rule would be implemented.

Mr. SHAYS. Give me a sense of how long that would happen.

Dr. MITCHELL. In this rule we're proposing 60 days.

Mr. SHAYS. And then it would take effect in 60 days?

Dr. MITCHELL. Yes.

Mr. SHAYS. And obviously there's a potential, particularly those involved in ruminant-to-ruminant feeding wanting to contest it in court, and that then that could stay it?

Dr. MITCHELL. Yes. This being a major rule, there are our review processes.

Mr. SHAYS. I have 5 more minutes of questioning. But I'd be happy to have Mr. Waxman speak, if you'd like a couple more minutes, then I'll begin.

Mr. WAXMAN. Mr. Chairman, I'm not going to take 5 minutes. I just want to say to this group, you're giving bureaucrats a good name. I think you've done an excellent job and I'm proud of the

work you've done in trying to protect the public from all the various aspects in which you're responding to this disease.

Dr. FRIEDMAN. Thank you. That's very nice of you. I appreciate that comment.

Mr. SHAYS. Dr. Friedman, just two basic questions. I'd like this for the record. The USDA has banned importation of beef products and cattle from countries that have BSE since 1989. I'd be interested to know why the FDA hasn't taken similar steps to ban the importation of bovine ingredients from BSE-affected countries in dietary supplements and cosmetics.

Dr. FRIEDMAN. Those products, there has been an import alert. There have been some shipments which have been stopped. That depends upon the quality of labeling of those products. But from the early 1990's we have had standard operating procedures in place and we have had import alerts to ban bringing those products in.

Mr. SHAYS. OK. One other question. Gelatin from BSE countries for animal use has been banned from the United States by USDA regulations, also 1989. And the FDA has no such ban for gelatin for use in human food and drugs. Is that the same response?

Dr. FRIEDMAN. I think it's a similar response. If I may, I will elaborate on that a little bit.

Again, the largest BSE population, the country most at risk, is the United Kingdom, and they have a prohibition on exporting gelatin made from BSE-infected native cows.

They are, however, taking bones and hides from BSE-free countries, making that into gelatin and then exporting that into a variety of places, including the United States. So even though that's called British gelatin, it is not from British cattle and therefore doesn't bear those risks that you might associate, unlikely or theoretical as those risks might be.

The World Health Organization, a number of other organizations, including USDA in their 1991 rule, based upon all the scientific information we had available, determined that gelatin was not a risky means of transmitting BSE, and so it's been sort of a world scientific opinion in that regard.

We are, however, for this product and for all products, vigilant. And should new information, new scientific information emerge, we want to take advantage of that.

Mr. SHAYS. OK. Thank you. And Dr. Gibbs, I'm concerned about the fact that the labs that do TSE are slated to close in 1998. Am I hearing proper information or not?

Mr. GIBBS. Perhaps I used the wrong terminology of closure. There's certainly a downsizing of our laboratory, but mainly because a number of scientists who were involved have left for other positions around the country.

I have been assured by the director of our institute that we will continue to be in business for several more years. We're currently being funded very handsomely, and NINDS is funding this field of transmissible encephalopathies to the tune of almost $7 million per year.

So our lab is not the only part that's working on this. Much of that would be in the extramural grant program. But it is my intention and it has been the assurance I've gotten from my director

that we will be in business for several more years, but not on the grandiose scale that we had been previously through the many years when we were developing this whole field.

Mr. SHAYS. Let me just ask, if any of you had wished that we asked a particular question that you wanted on the public record, tell us what the question was and answer it. But I'm not looking for a long response because we're going to get to our next panel, but if there's anything that needs to be part of the record.

Mr. GIBBS. One thing, Mr. Chairman, in your opening remarks you talked about diagnostic tests not being available. I will submit for the record a paper that we just published in September on the development of a diagnostic test for the spongiform encephalopathy agent, particularly in humans but also in cattle and in sheep, using spinal fluid as a mark—there is a marker in spinal fluid. And this test is now being put in the hands of our technology transfer organization at NIH.

Mr. SHAYS. Do any of you wish to make a closing comment, or we'll get on with our next panel.

Dr. FRIEDMAN. May I only thank you and the committee members for the thoughtful and courteous way that you've conducted this hearing.

Mr. SHAYS. You're not surprised, are you?

Dr. FRIEDMAN. No, sir. Pleased but not surprised. We just hope it continues.

Mr. SHAYS. Thank you. It was wonderful to have all of you here. And we will get on with our next panel.

Mr. SHAYS. Our second panel is William Hueston, who is from the Virginia-Maryland College of Veterinary Medicine, and Frank Bastian, who is from the University of Southern Alabama School of Medicine.

I ask both individuals to come, and we will swear you in.

We will have a 5-minute recess so people can move back and forth.

[Recess.]

Mr. SHAYS. We have William Hueston and Frank Bastian. I will swear you in.

[Witnesses sworn.]

Mr. SHAYS. On administering the oath, both witnesses before the committee have responded in the affirmative. And Dr. Hueston, I will call you first.

You all have prepared statements, if in the process of hearing the comments made before you want to amend your statement or add to it, feel free. We like the witnesses who follow, both of you were here, to comment on what was said if you think that's necessary so we don't even have to ask it. OK?

Dr. Hueston.

STATEMENTS OF WILL HUESTON, D.V.M., VIRGINIA-MARYLAND COLLEGE OF VETERINARY MEDICINE; AND FRANK O. BASTIAN, M.D., UNIVERSITY OF SOUTHERN ALABAMA, SCHOOL OF MEDICINE

Mr. HUESTON. Thank you. My name is Will Hueston. I am here as a veterinary epidemiologist, and my background, I have been involved in the study of bovine spongiform encephalopathy now for

7 years, beginning as a public servant, an employee of the U.S. Department of Agriculture doing risk analysis work on the likelihood of us seeing bovine spongiform encephalophy in the United States.

I have also spent 6 months assigned to the epidemiology unit in 1991 investigating BSE in Great Britain. I have served on advisory committees for the International Office of Epizootics and World Health Organization, and then most recently was appointed by the British Government as a member of their Spongiform Encephalopathy Committee and still serve in that capacity.

I appreciate your opening remarks. This is a most challenging disease. It has been identified as being a common source epidemic, a feed-borne, an animal feed-borne epidemic traced to the incorporation of ruminant-derived animal proteins. And it is also an area where there is a tremendous amount of ongoing scientific debate so that on a weekly basis there is new information arriving.

Mr. SHAYS. I am going to ask you to move the microphone closer to you. You can move the ice pitcher if you want. Thank you.

Mr. HUESTON. Thank you. So here we have a new and emerging disease on which there is new information weekly, and the challenge for the agencies involved, animal and public health agencies and the affected industries and producers is how does one make rational policy in the face of this ongoing, changing scientific information. And I would like to propose to the committee that risk analysis is the tool for reaching those rational decisions.

Essentially, risk analysis involves identifying hazards, what could go wrong; assessing the likelihood that those things may go wrong, and the magnitude of the impacts should they go wrong; evaluating or elucidating risk management options, what are the opportunities that we have to reduce the likelihood of something going wrong or to minimize the impact should it go wrong; and last, risk communication. And risk communication involves incorporating all the potentially affected parties in the entire process of considering the evidence, evaluating options, and assessing our strategies.

The options for the control of bovine spongiform encephalopathy focus first and foremost on animal feeding. The source and hazards you've identified and explained quite nicely. Certainly, we have the imports of animals and potential materials going into feed from Great Britain and we have the indigenous sources.

We have the opportunity of controlling and the second step through inactivation of these materials. Unfortunately, the information to date says this agent is very, very difficult to inactivate. Last, we have the opportunity to look at how we use the material or the finished product to avoid exposure to susceptible animals.

Now, having said this, there is multiple different options in which one can put together these risk management strategies to achieve the end goal of managing risk. The proposed rule that's being discussed today, the proposed final rule is scientifically sound.

From my experience, it focuses on use and looks on use to finish product, the sourcing. If the material has ruminant-derived protein or mink-derived protein, then those materials are limited in their potential use, and that use restriction goes from both the renderer

to the blender to the feed manufacturer to the establishment and individuals feeding cattle.

I think the flexibility that is built into the rule is laudable, this flexibility that says and allows that as new information becomes available, it provides the flexibility to respond to that new information in a very prompt and expeditious manner. I would like, for the benefit of keeping this short and to the point, to share with you a few of the observations that I bring from my involvement with the British experience.

First, the science and the art of effective disease prevention and control must be practical and implementable. Disease prevention and control cannot occur by regulation alone, and there exists no enforcement authority large enough or effective enough to enforce regulations that people don't want or understand the implications. So the challenge here is to come up with a consensus among all of the affected parties on the ideal, scientifically sound management protocols and to move ahead to implement them.

Again, we, as human beings, operate under two mutually exclusive paradigms. One being an ounce of prevention is worth a pound of cure, contrasted with if it ain't broke, why fix it. And that's part of the situation we face here today. As speaker after speaker reiterated, we do not have bovine spongiform encephalopathy in the United States.

My second lesson or experience is that we absolutely need practical and applied research, as well as basic research. So while one group of scientists debates the characteristics of the etiologic agent, my focus as an epidemiologist is given the information we have, how can we control, manage, minimize the risks to animal and human health. And that means we need research dollars focused on issues like surveillance and inactivation and alternative uses of this material that's generated, this ruminant-derived protein. There is a tremendous opportunity to collaborate with researchers in other countries. I think this is a golden opportunity to let drop any limitations on that investigation.

The third is that I want to reiterate a comment made by some of the other speakers. I applaud the coordination and collaboration that's in evidence here between the animal and public health agencies. I think this is unique. This was not the initial characteristic in Great Britain. There was not an active communication between the human and animal health agencies. It led to a lot of misunderstanding, a great deal of mistrust, and I think potentiated the challenge that they are currently facing.

Finally, a sobering note. If, in the end, our prevention is successful, it is effective and we never see BSE in the United States, then all of the preventive measures that have been put in place will be criticized as unnecessary. If, on the other hand, we see a case of BSE in the United States, then obviously the prevention, it will be too late to prevent its occurrence, and the same individuals will be criticized, the same agencies will be criticized for not taking appropriate actions. And we will join Great Britain, France, Switzerland, Ireland, and Portugal in trying to rebuild our national image and

trying to recapture the trust through verification with our trading partners, and last, in trying to reestablish our reputation as a world leader in providing an abundant, high quality and affordable safe food supply. Thank you.

[The prepared statement of Mr. Hueston follows:]

Testimony by

William D. Hueston, DVM, PhD

Professor and Associate Dean

Virginia-Maryland Regional College of Veterinary Medicine

University of Maryland at College Park

Before the

Human Resources Subcommittee

Committee on Government Reform and Oversight

House of Representatives

January 29, 1997

Thank you for the opportunity to participate in today's hearing. My name is Will Hueston. I am a veterinary epidemiologist. I study the patterns and risk factors of disease for the purpose of identifying effective and practical prevention and control strategies. I have been involved in the study of Bovine Spongiform Encephalopathy (BSE) for the past 7 years, first as a public servant with the US Department of Agriculture and now as Professor and Associate Dean for the University of Maryland campus of the Virginia-Maryland Regional College of Veterinary Medicine. My work has included risk analysis of the potential for BSE appearance in the United States, evaluation of surveillance systems for the detection of BSE and identification of risk management strategies to prevent and control BSE. I spent 6 months in the United Kingdom in

1991 assigned to the BSE investigation team. I have provided advice to producers, professional organizations, industry and governmental agencies on the prevention and control of BSE. I have served on expert consultations on BSE for both the International Office of Epizootics (OIE) and the World Health Organization (WHO). Currently I serve as a member of the Spongiform Encephalopathy Advisory Committee (SEAC) for the British government. My comments today will focus primarily on BSE.

Bovine spongiform encephalopathy exemplifies the challenges of new and emerging diseases. First identified in 1986, the disease has reached epidemic proportions in the United Kingdom. Epidemiologic investigations have revealed a common factor among all of the BSE affected herds, the incorporation of meat and bone meal into the cattle feed. Therefore, BSE represents a large animal feed related epidemic, or in epidemiologic terms, an extended common source epidemic. Research into the cause and course of this disease and other transmissible spongiform encephalopathies continues at a furious pace in laboratories around the world. We are witnessing the scientific method in action, as various hypotheses are proposed and debated. This subcommittee has the challenging task of considering federal agencies' response to potential threats of transmissible spongiform encephalopathies while new scientific information is appearing almost weekly.

Risk analysis has emerged as a tool for making rationale decisions for disease prevention and control in the face of uncertainty and changing knowledge. Risk analysis comprises hazard identification (what can go wrong); risk assessment (how likely is this to go wrong and what are the consequences); risk management (what are the options for effectively reducing the likelihood

of something going wrong and lessen the impact); and risk communication (involving the potentially affected parties in the whole process of hazard identification, risk assessment and risk management). The US response to potential threats of transmissible spongiform encephalopathies must be based on sound risk analysis.

Therefore, management of the potential threats of BSE must focus on current knowledge on the source of potential infection and the primary means of spread of the disease, namely incorporation of infective materials in cattle feed. Applying risk analysis, one must evaluate the entire animal feeding system from the raw materials to the processing and treatment of these materials and finally, the uses made of the resulting products. The most important of the potentially infective raw materials are infected tissues from animals and animal products imported from the United Kingdom and other BSE-infected countries. Potential indigenous sources of known transmissible spongiform encephalopathy agents include infected tissues from sheep, mink and wild ruminants infected with scrapie, transmissible mink encephalopathy and chronic wasting disease, respectively. Complete exclusion of all of these infected tissues from ruminant feed represents one approach to reduce the potential risk of BSE in the US. Additionally, exclusion of those cattle tissues shown in Great Britain to contain BSE infectivity, ie, brain, spinal cord, retina and distal ileum, provides extra insurance against any silent infections or heretofore unidentified cattle TSE. Another risk management approach would be implementation of a process which effectively inactivates transmissible spongiform encephalopathy agents, regardless of the source. Even if infective tissues enter the system, the agent would be inactivated. Research results to date suggest that inactivation of TSEs is very difficult. The third approach for risk management involves the uses of the products. Restricting or redirected materials to uses which do not expose

susceptible animals will prevent and control transmission. Additional risk management approaches involve blending of components of two or more of the aforementioned strategies, for instance, excluding diseased animals from the rendering process and disallowing the use of ruminant-derived animal proteins in ruminant feeds.

The most effective risk management strategies integrate multiple safeguards to provide extra assurance that the potential risks are reduced. These combination strategies compensate for potential weaknesses in any one of the prevention steps and add further protections in the event of the failure of a single step.

The proposed final rule on the ruminant to ruminant feed ban is scientifically sound. The rule focuses on the use of ruminant-derived protein and integrates use restrictions at several levels: the renderer, the blender, the feed manufacturer, the distributor, and the establishments and individuals feeding ruminants. Laudably, the proposed final rule incorporates flexibility to accomodate new scientific findings and manufacturing approaches. Lastly, the proposed final rule employs a very pragmatic approach to record-keeping, by utilizing invoices and receipts to document compliance.

Before I close, let me make a few observations based on my experience with the British handling of BSE. First, developing and implementing effective disease prevention and control is both a science and an art. The ideal system must be practical and implementable. Disease prevention and control will not occur by regulation alone as clearly demonstrated by the British experience. Further, the best enforcement system in the world cannot ensure that the prevention system is

working if the affected parties do not understand and collaborate. We live by two mutually exclusive paradigms: "An ounce of prevention is worth a pound of cure" and "If it ain't broke, don't fix it". Every effort should be made to reach a concensus among all of the affected parties that these preventive measures are scientifically justified, pragmatic and implementable.

Second, research must be directed at the practical and applied issues involved in preventing these diseases as well as the basic science. Development of effective surveillance strategies, the search for means of inactivation, and investigation of alternative uses for ruminant proteins need to be research priorities. Great Britain is playing catch-up now on a number of research fronts. Again, justifying a research priority for a disease that does not occur in the US sounds like an oxymoron. We have tremendous opportunities to collaborate with researchers in other countries to address these issues.

Third, the committee should applaud the high degree of coordination and collaboration evidenced by all of the federal agencies involved with the transmissible spongiform encephalopathies. The lack of coordination between animal and public health agencies in Great Britain exacerbated the problem.

Finally, we must recognize that if the preventive measures taken by the US are effective, then they will be criticized as unnecessary. On the other hand, if BSE occurs in the US, we will be criticized for not taking enough preventive action and we will join Great Britain, France, Switzerland, Ireland and Portugal trying to rid our country of this disease and regain our reputation as the world's leader in the production of abundant, affordable, high quality and safe food.

Mr. SHAYS. Thank you, Doctor, for your observations.

Dr. Bastian.

Dr. BASTIAN. I appreciate the opportunity to participate in this hearing of the Committee on Government Reform and Oversight regarding Federal agencies' response to the potential threat of transmissible spongiform encephalopathy. I have been working for over 20 years in this field.

I am a professor of pathology, M.D., and practice neuropathology at the University of South Alabama where I have served as a consultant for the diagnosis of Creutzfeldt-Jakob disease from tissues submitted to me from other institutions all over the United States.

I have been involved in research on the transmission of spongiform encephalopathy regarding the nature of the transmissible agent. In 1984, I was visiting professor in the laboratory of Tony Palmer at the University of Cambridge in England for the purpose of studying scrapie. At that time I visited with Drs. Dickenson, Somerville and Fraser at the Neuropathogenesis Unit in Edinburgh where I presented my research data and reviewed their experience with scrapie mouse models, and I presented lectures at seven institutions during my visit to the U.K.

In 1991, I published a book entitled, "Creutzfeldt-Jakob Disease and Other Transmissible Spongiform Encephalopathies." In 1992, I held a symposium on bovine spongiform encephalopathy or mad cow disease at the American Society of Microbiology general meeting in New Orleans. In May 1996, I presented at the Duma Foundation of Infectious Disease Symposium on Emerging Infections held at the National Press Club in Washington, DC.

Subsequently, I was invited to present my findings at the USDA advisory committee meeting in Ames, IA, in June, and in December 1996, I was an invited speaker for discussion of the state-of-the-art of the science at the CERES international symposium on the transmissible spongiform encephalopathies.

Now, my assignment today is to deal with the effectiveness of the agencies in their handling of research funding and control measures relating to the transmissible spongiform encephalopathies, which I will refer to as the TSEs. The TSEs include scrapie in sheep and goats, transmissible mink encephalopathy, bovine spongiform encephalopathy, and Creutzfeldt-Jakob disease in humans, otherwise referred to as CJD.

I will begin by pointing out that the agencies have been stymied by the fact that, one, the identity of the transmissible agent of the TSE is not known; two, there is no preclinical test for TSE agent; three, the epidemiology of TSE is not known; and four, the susceptibility to TSE is not known.

There are a limited number of theories regarding the nature of the transmissible agent. First, the prion or replicating protein theory which suggests that abnormal folding of the host protein is the cause, is not consistent with basic concepts in biology wherein DNA or RNA is required for replication.

At a recent international symposium, researchers presented evidence that the folding of the protein as proposed by Dr. Prusner does not occur. The numerous strains evident in TSE are more consistent with an agent possessing it's own genome. The recent paper in science is significant in that the authors found that the prion is

not necessary for infection and instead is a product of the infection rather than being the causal agent.

The concept I propose is that there is a wall-less bacteria involved in the pathogenesis of TSE. In 1979, I reported spiroplasma-like occlusions from the brain biopsy of a patient with Creutzfeldt-Jakob disease. Spiroplasmas are present in the hemolymph of most insects and several strains are known to experimentally induce spongiform encephalopathy in rodents.

We have demonstrated that spiroplasma proteins cross-react with TSE antibodies. In fact, the unique fibril proteins within spiroplasma are identical morphologically to fibrilproteins consistently seen in TSE tissue preparations and not in controls. Recently, we have documented the presence of a molecute gene in Creutzfeldt-Jakob brain tissues with a 97 percent homology to spiroplasma. The spiroplasma concept fits the epidemiology chain as evidenced for TSE and as no other theory does. This concept should be further investigated.

The emphasis placed totally on the prion theory by the scientific community over the past 15 years to the point of exclusion of all other theories has frustrated any realistic attempt to develop a preclinical test for TSE, the lack of which has resulted in incomplete knowledge of the epidemiology of TSE.

CJD has a worldwide occurrence with one to two cases seen per year in a town the size of Mobile. Only 250 CJD cases occur each year in the United States. I suspect that the incidence of the disease is much higher. Furthermore, research efforts have been concentrated on molecular biology studies without regard to our basic lack of understanding of the pathogenic mechanisms involved in TSE. The agencies have fallen short in the handling of these matters.

In an effort to search for the agent, they have placed almost all of their funding in one basket. I've heard that at least $75 million has been given to one research laboratory in the past 15 years. My opinion is that this has not been money well spent since we appear no closer to resolving the identity of a TSE agent from that effort.

This lack of progress has impaired efforts to develop a preclinical test nucleic which is necessary to have a lead on either an agent-specific acid or a protein. The prion is now realized to be simply a reaction product of the infection. In regard to epidemiological studies that have settled on using death certificates, which are totally unreliable, the clinical diagnosis is wrong in at least 25 percent of cases. We have no idea of the extent of the disease in this country, much less the distribution of the agent. I have pushed for making CJD reportable, but the agencies are only interested in crises, particularly whether the new variant of CJD has arrived in this country. I disagree with that approach.

The revelation of possible contamination of blood products by CJD-infected professional blood donors has been handled by the agencies by massive withdrawals of blood products. I question the wisdom of this Band-Aid treatment alone. Since we are still 10 years away from recombinant DNA production of blood clotting factors, the current methodology of filtration of blood products is likely inadequate to protect us from contamination and we are waiting for the ax to fall again.

Recommendations. I suggest that we do not try to blame the prior handling of the TSE problem by the agencies, especially since we are now enlightened by evidence indicating that the dogma is wrong. Let's move forward.

I would like to make the following recommendations: One, in regard to funding of research efforts, we should pursue all clues available regarding the nature of the agent. The money should not all be given to one or two laboratories, but should be spread out to provide for some fresh approaches. The primary aim of the research should be to develop a preclinical test.

In addition, there should be funds for studying basic pathogenic mechanisms in an animal model. I believe the immune system is very important in the pathogenesis of TSE and should be investigated. Levels of funding must be increased to encourage other researchers to enter the field. The problem will be more likely to be solved if we encourage participation by scientists from multiple disciplines. The rarity of the disease has hampered getting the attention of many scientists in the past, since most Ph.D.'s must search out funding with a reasonable probability of getting it.

My second recommendation, in regard to epidemiological studies, we must avoid the crisis management approach previously used by the agencies, and instead try to get a handle on the prevalence of CJD. I believe that CJD and the other TSEs should be reportable. Identification of the patients early on in their illness would provide researchers the opportunity to apply new diagnostic tests or therapeutic measures. The other approach would be to develop a clinical center for CJD patients thereby concentrating clinical data on a rare disease.

In conclusion, my request is that you pursue some new directives with haste, since there is at least a dangerous theoretical threat of TSE from our blood supply and food, particularly beef products. Funding is necessary to search out the transmissible agent, which could lead to development of a much needed preclinical test, even an immunization program. New research avenues should be pursued in light of recent scientific revelations.

I thank you for your interest.

[The prepared statement of Dr. Bastian follows:]

TESTIMONY OF FRANK OWEN BASTIAN, M.D.
UNIVERSITY OF SOUTH ALABAMA

INTRODUCTION:

I appreciate the opportunity to participate in this hearing of the committee on government reform and oversight regarding federal agencies response to the potential threats of transmissible spongiform encephalopathies (TSE). I have been working for over 20 years in this field. I am a professor of pathology and practice neuropathology wherein I have served as a consultant for diagnosis of CJD from tissues submitted to me from other institutions all over the United States. I have long been involved in research on TSE regarding the nature of the transmissible agent. In 1984 I was a visiting professor in the laboratory of Tony Palmer at University of Cambridge, England for the purpose of studying scrapie. At that time, I visited with Drs. Dickinson, Somerville, and Fraser at the Neuropathogenesis Unit in Edinburgh where I presented my research data and reviewed their experience with scrapie mouse models. I presented lectures at seven institutions during my visit to the UK.

In 1991, I published a book entitled **"Creutzfeldt-Jakob disease and other transmissible spongiform encephalopathies"**. In 1992 I held a symposium on "Bovine spongiform encephalopathy" (BSE) at the American Society of Microbiology general meeting in New Orleans. In May, 1996, I presented at the Duma Foundation of Infectious Disease Symposium on "Emerging Infections" held at the National Press club in Washington, DC. Subsequently, I was invited to present my findings at the USDA advisory committee meeting on Scrapie/BSE in Ames Iowa in June, 1996. In December, 1996, I was invited speaker for discussion of THE STATE OF THE ART OF THE SCIENCE at the CERES international symposium on "the transmissible spongiform encephalopathies".

BACKGROUND:

On March 20, 1996, Will reported 10 cases of a new variant of Creutzfeldt-Jakob disease (vCJD) which occurs in a youthful population (16 to 35 yrs). An older population is susceptible to sporadic CJD with a peak age of 65 years. The vCJD cases were distinctive from the usual CJD case in that they present with psychiatric symptoms and have a longer clinical course. The neuropathology of the vCJD cases is also unique and it is this pattern created in Macaque monkeys following inoculation of the BSE agent that confirms a link between BSE and human disease. Furthermore, the infection-specific protein (PrPres) seen in all cases of transmissible spongiform encephalopathy shows a unique pattern of binding of sugar moieties in vCJD cases similar to PrP derived from BSE-infected cattle or BSE-infected cats but which is distinctly different from sugar binding properties of PrP associated with sporadic CJD.

Clearly this signature of the BSE agent further confirms the link of BSE to vCJD cases. The crossing of BSE into humans presumes a highly virulent TSE strain which likely evolved from feeding cattle cattle offal, especially since serial passage of the CJD agent in hamsters led to shortening of the incubation period from 467 days to 216.5 days.

Although we are currently very concerned about the vCJD agent and whether it may occur in the United States, the sporadic form of CJD occurs here at a rate of 1 to 2 cases per year in a small city the size of Mobile. Approximately 250 cases occur in the United states every year. CJD is a uniformly fatal disease with 90% of patients dying within one year, most cases within 6 months. A rarer familial form of the disease (5% of CJD cases), shows autosomal dominant transmission. The histopathology of CJD is characterized by spongiform encephalopathy, proliferation of hypertrophic astrocytes, and occasionally, focal deposits with tinctorial properties of Amyloid (15% of CJD cases, but consistently observed in familial CJD). These amyloid-like plaques are of special interest since identical amyloid plaques surrounded by vacuolated neuropil are seen in brain tissues from patients with the new variant of CJD (vCJD) recently reported in England.

The spongiform encephalopathy of CJD is distinctive and when Hadlow reported in 1959 a comparison between the pathology of scrapie, kuru (a fatal degenerative brain disease among the Fore people of eastern New Guinea) and CJD, it was obvious to try to transmit CJD to animals by inoculation. Scrapie had been known for over 200 years and had been well established as a transmissible disease of sheep, that is inoculation of brain tissues from one animal into another produced the disease. Both kuru and CJD were subsequently passaged to chimpanzees.

Since then, there have been numerous instances of reported accidental transmission of CJD via corneal or dural transplants utilizing cadaveric tissues. In the 1980's, CJD developed in young people in this country who had received therapeutic administration of growth hormone obtained from cadaveric pituitary glands, with incubation periods of 8 years duration. Transmissible spongiform encephalopathy was recognized in other animal populations as transmissible mink encephalopathy (TME) and bovine spongiform encephalopathy (BSE). It is noteworthy that scrapie shows a wide variation in topography of the spongiform changes and varying incubation times suggesting involvement of multiple strains of the transmissible agent, whereas BSE has a uniform neuropathological pattern suggesting a single strain.

Definitive diagnosis of these diseases can only be made by histologic examination or PrP determinations in infected brain tissues. Other screening methods proposed include an immunoassay for 14-3-3 protein in spinal fluid (CSF) which is positive in 96% of CJD cases, but is false-positive in Herpes encephalitis or following a recent stroke. This CSF test becomes positive just before onset of clinical disease and is of no practical value in developing a preclinical test for screening blood donors or impending infection in BSE herds.

NATURE OF THE TRANSMISSIBLE AGENT OF TSE:

The transmissible agents of scrapie and CJD are relatively large, the size of a medium size virus (>25 nanometers) and sediment on sucrose gradients primarily within the microsomal fraction. The scrapie agent shows marked resistance to radiation and survives high temperatures, although 100°C kills 99% of the scrapie agent in 1 minute with complete sterilization of scrapie-contaminated material by steam autoclaving at 132°C for 60 minutes. This suggests that only a small agent subpopulation shows unusual resistance to physical and chemical treatment. Nevertheless, the resistance of the transmissible agent to these treatments poses the most problematic area for the rendering industry.

Following experimental inoculation of scrapie into rodents, the agent replicates in the reticuloendothelial system and undergoes a hematogenous phase, before eventually localizing to brain. The persistence of scrapie infectivity in lymphoid tissues of sheep, including tonsils, along the Gastrointestinal tract suggests the oral route is a significant portal of entry. Oral transmission of CJD has been shown in nonhuman primates. Although tissues from Scrapie or CJD infected animals, for the most part, show no evidence of gross inflammatory reaction, there is significant microglial proliferation and T-lymphocyte recruitment in mouse scrapie-infected brains long before onset of clinical symptoms. The inefficiency of producing scrapie infection in the severe combined immunodeficiency mouse shows the importance of the immune system in the pathogenesis of TSE.

THEORIES REGARDING THE NATURE OF THE CAUSAL AGENT:

There are a limited number of theories regarding identity of the causal agent.

THE PROTEIN ONLY THEORY (PRION)

Prusiner proposed that TSE is caused by abnormal folding of a host cell protein (PrP) either occurring de novo or by close interaction with another "infectious" abnormally transformed protein called the prion. The abnormal isoform is presumably responsible for the central nervous system dysfunction and neuropathology. A single amino acid difference in a mutated PrP molecule determines which population of neurons is vulnerable and therefore, the resulting clinical syndrome. A common substitution of Methionine to Valine, associated with PrP codon 129, is found in inherited, iatrogenic and sporadic forms of CJD. Prusiner suggested that the transformation may involve the interaction of as yet unknown chaperon protein. The lack of evidence of scrapie-specific nucleic acid and the resistance of the agent to UV radiation in the presence of Psoralens was put forth as the primary evidence supporting the protein only hypothesis.

There is a large body of data to indicate that PrP itself is insufficient to transmit CJD. No infectivity has been demonstrable with purified, recombinant or transgenic PrP protein. There is also abundant evidence that the prion can be dissociated from infectivity. For example Amphotericin B treatment of hamsters infected with scrapie significantly delays buildup of PrPres but does not inhibit increase in infectivity thereby dissociating the protein from infectivity. Furthermore, there is some question regarding interpretation of data used to show that the agent of TSE has no nucleic acid component since viruses (i.e., polic) and spore forming bacteria (i.e., *Bacillus subtilis*) are resistant to the penetration of psoralen and therefore are not susceptible to UV radiation. Recently, the folding of the prion speculated by Prusiner to account for the strain diversity has been shown by NMR studies not to occur.

An additional problem for the prion theory is the recent induction of scrapie-like spongiform encephalopathy in mice by inoculation of hay mites obtained from endemic areas suggesting that an unknown factor is involved in the production of the disease. The PrP gene has not been found in the mite preparations. The recent Science article has clearly demonstrated that PrPres is not the causal agent of TSE and suggests that PrP is a product of the infection. One fallacy of the prion concept all along has been the tendency to further modify the theory with each additional piece of evidence, which is essentially Occam's razor in reverse. I worry that rather than discard the theory since it does not fit the chain of evidence, the Prion advocates will simply expand the theory to incorporate the new data and further confuse the issue.

A BACTERIUM AS THE CAUSE OF CJD:

We became interested in a more conventional microbial etiology for CJD upon discovering a spiral-shaped organelle present in neuronal cell processes in a CJD brain biopsy but not in normal brain samples. This observation was later confirmed by us and two other laboratories. The morphology of this organelle was reminiscent of spiroplasma, a cell-wall-less microorganism related to Mycoplasma. Spiroplasma are small pleomorphic organisms, consisting of coccoid, filamentous and spiral forms. They along with mycoplasmas have the smallest genome known for any free-living organism. Spiroplasmas are fastidious and require enriched medium for growth. They are present in the hemolymph of most insects, and abound in the salivary glands of vector insects that transmit plant diseases. Spiroplasmas contain both DNA and RNA and possess all the machinery of protein synthesis. Although most Spiroplasmas known to exist by microscopic observation are not cultivable, 26 serologically distinct groups have been grown *in vitro*. Spiroplasma of different strains show a great deal of biological diversity and we have shown spiroplasma to be resistant to fixatives and near boiling temperatures.

We initially tested the hypothesis that spiroplasma may cause a TSE-like degenerative brain disorder in a rat model. We used a rabbit tick isolate that grew weli at mammalian body temperature. The experimental *Spiroplasma* infection roduced microcystic changes in the rat brain that closely resembled the spongiform alteration of

TSE. Electron micrographs of spiroplasma-infected brain tissues were essentially identical to the pathology seen in CJD. Vacuolization without inflammation was seen at 8 weeks in this study and *Spiroplasma* were shown by immunocytochemistry to localize to neurons. Spiroplasma have produced persistent brain infection in rodents and have been isolated over 800 days following inoculation yet blend into the tissue background making them unidentifiable by electron microscopy.

A characteristic and, in fact, diagnostic feature of CJD and other TSEs is the presence of unique fibrils seen by electron microscopy in homogenized/protease-treated infected brain tissues. These structures, designated *scrapie-associated fibrils* (SAF) since they were first described in experimental scrapie, are distinctive from the usual twisted amyloid fibrils and, even though they are protease resistant, are not composed of PrP. SAF accumulates in tissues in direct proportion to infectivity, so that they likely represent a part of the infectious agent. **Several investigators, including ourselves, have identified fibrils in spiroplasma that appear morphologically identical to SAF**. The spiroplasma fibrils were shown in our studies to be protease resistant and have been found in disrupted/protease-treated spiroplasma-infected rat brain preparations.

Another piece of intriguing evidence connecting spiroplasma to TSE is the cross-reactivity of scrapie antibody with *Spiroplasma* proteins. Anti-scrapie polyclonal antisera, raised against protease-resistant proteins (including prion proteins) from scrapie strain ME7 infected mouse brains (Courtesy- Richard Rubenstein), was tested by Western blot against a protease-resistant extract of *Spiroplasma mirum* grown *in vitro*. Four spiroplasma protein bands reacted with this antisera, indicating that there is at least one protease-resistant protein in scrapie brains that cross-reacts to several *Spiroplasma* protease-resistant proteins. These results suggest that spiroplasma antigens are present in the scrapie tissues. Similarly, disrupted hay mites from Icelandic fields which induce scrapie when inoculated into mice, show the presence of cross-reacting antigens to scrapie antisera. The PrP cross-reacting bands in the mite preparations are present at 60 kDa, 40 kDa, 27 kDa with several lower bands. I propose that the hay mites likely contain spiroplasma as normal flora, thereby accounting for the cross-reactivity to the scrapie antisera. These data would be consistent with a spiroplasma being the cause of this experimental TSE mouse model.

Recent and more compelling evidence supporting a spiroplasma etiology for CJD was the discovery, by Polymerase Chain Reaction (PCR) analysis, of Mollicute 16S ribosomal RNA gene sequences in CJD brain samples. We designed two oligo-nucleotides suitable for PCR analysis from conserved sequences present in Spiroplasma and Mycoplasma 16S rRNA genes. These primers amplify 1 kb fragments from both Mycoplasma and Spiroplasma DNA preparations (**Figure 1**). Because 16S rRNA sequences are well conserved among related microorganisms, we predicted that they should amplify the relevant portions of genes encoding 16S rRNA from Spiroplasma or other phylogenetically related Mollicutes. We then used these primers to screen CJD brain extracts for the presence of Mollicute 16S rDNA sequences. Even

though only a limited number of samples were screened, a 1 kb fragment was successfully amplified from two CJD samples but not from controls. The 1 kb PCR product from spiroplasma hybridized on Southern blot with spiroplasma DNA, mycoplasma DNA, and DNA from two CJD cases, but not with DNA from Alzheimer brain (Figure 2). The 1 kb product amplified from CJD brain sample was subsequently cloned and 300 base pairs sequenced. A DNA homology search using the GenBank database revealed the cloned sequence exhibited 95 to 97 % homology to Mycoplasma and Spiroplasma 16S rRNA genes. Clearly, Mollicute DNA was present in those CJD samples.

Figure 1

PCR Using Mollicute Gene Primers

mrks 6 Different CJD Cases MYC SPIR

! 1 2 3 4 5 6 ! !

+ + + +

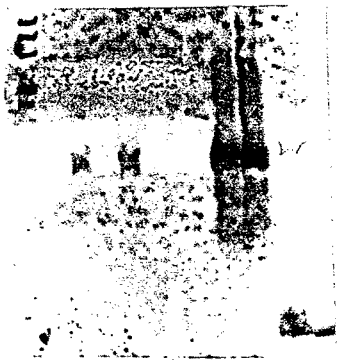
Figure 2

Hybridization Using Spiroplasma PCR Product

mrks Different CJD Cases Myc Spir N Alz

! 1 2 3 4 5 6 ! ! ! !

+ + + +



ROLE OF AGENCIES IN HANDLING TSE PROBLEM:

My assignment is to deal with the effectiveness of the agencies in their handling of the TSE problem as it relates to 1) ruminant to ruminant ban; 2) food safety; 3) blood product safety; and 4) funding.

I will begin by pointing out that the agencies have been faced by several serious problems relating to TSE. These include **1) the identity of transmissible agent is not known; 2) there is no preclinical test for the agent; 3) the epidemiology of TSE is not known; and 4) the susceptibility to TSE is not known.**

ACTIONS OF THE NIH

The biggest burden which has impacted on the efficiency of other agencies in handling this problem has been the funding of research efforts to search out the causative agent of TSE and therein provide the basis for a preclinical test for this disease. Unfortunately, they have place most all their funding in one basket. I've heard that at least $ 75 million dollars has been given to one research laboratory over the past 15 years. It is my opinion that this has not been money well spent since we appear no closer to resolving the identity of the TSE agent from that effort. This lack of progress has impaired efforts to develop a preclinical test where it is necessary to have a lead on either an agent specific nucleic acid or protein. The prion is now realized to be simply a reaction product of the infection.

In regard to my personal experience in obtaining NIH funding, I received a grant to study the neuropathology of experimental Spiroplasma infection in the rat model in 1982. At that time this was the only research grant funded on Spiroplasma in the United States. We published our findings in the American Journal of Pathology wherein we showed the marked similarity of the spongiform neuropathology of experimental Spiroplasma infection to that of CJD. In our reapplication in 1984, we presented exciting data showing other links between Spiroplasma and CJD including 1) the morphological identity of the unique Spiroplasma fibril proteins to scrapie associated fibrils which had become pathognomonic for TSE; 2) the immunological cross-reactivity of anti-scrapie antisera with Spiroplasma proteins; and 3) additional supporting morphological evidence including Golgi studies showing the marked similarity of the neuropathology of experimental Spiroplasma infection in the rat model to CJD. This grant and others were turned down by the NIH study sections with the comment that the problem was solved and that the Prion was the causal agent. Later applications suggested that Bastian has proposed this theory for years and the fact that he has not proved it yet indicates that he is wrong. It is unbelievable that Scientists were willing to accept the Prion theory without question even though it was heretical in the sense that there had been no previous documentation of a replicating protein in the field of Microbiology.

When I visited Washington DC to present at the Duma sponsored symposium in May, 1996, I decided to meet with NIH administrators and discuss funding priorities in the field. I was disappointed when I contacted NINCDS officials who told me that my research was not in sinc with current scientific thinking and that they preferred not to meet with me. I did arrange presentations to NIH administrators in the blood section and infectious disease section. Although encouraging in their comments, they have

been sluggish to respond to the need to rapidly expand efforts in this area with only temporary small grant programs available ($50,000). I was encouraged to submit a preliminary research proposal to the blood section in December, 1996 but have not heard back. I have subsequently submitted a research grant to the USDA for consideration in their January call for applications regarding food safety.

ACTIONS OF THE FDA

The actions of the FDA in monitoring food safety has been stymied by the lack of a preclinical test for this disease. Also the lack research into basic studies of a model system has forced the agency to make uninformed decisions. Even so, I am surprised that the FDA is willing to push forward without regard to consulting all of the expertise available.

In 1995, when meetings occurred in Washington in regard to possible contamination of our blood supply from professional blood donors who later developed CJD, I went to the meetings at my own expense. At these meetings I presented my credentials as an expert in the field and offered my services in dealing with this evolving problem. I have since been ignored by the FDA and not invited to subsequent meetings.

Be that as it may, the handling of problem by the FDA was at best a band aid approach. Data presented at the meeting indicated that hemophiliacs had a 100% chance of coming in contact with a possible TSE contaminant. Professional blood donors can give up to 70 units of plasma per year which is pooled into massive lots for clotting factor production. Experimentally, the agent is transferred from blood, although there is little basic data regarding the potential danger because of lack of a well studied disease model. The recommended withdrawal of $50,000,000 of blood products could only be a temporary remedy for the situation since we still have no adequate methodology for detection or control of the TSEs.

PUBLIC HEALTH SERVICE ACTIONS:

THE CDC: The CDC conducts surveillance for CJD through examination of death certificate data compiled by the National Center for Health Statistics. Their results indicate that the annual CJD mortality rates have remained stable at approximately 1 per million with deaths in persons younger than 30 yrs of age to be extremely rare (<5 cases per billion per year).

This mechanism of obtaining data is grossly inadequate. The clinical error in diagnosis for CJD is >25%. Diagnoses placed on the death certificates at time of death are not updated even following contradictory autopsy findings. There is also a tendency for physicians to minimize the seriousness of the disease thereby avoiding

publicity in order to allow patients to be admitted to nursing homes, relieving hospitals of long term care responsibilities and the family of unwanted financial burden if specialized care were necessary. Most nursing home personnel are not well versed in the dangers of caring for CJD patients, the emphasis on the need for specialized care and precautions would dissuade their willingness to admit CJD patients. Physicians not reporting the disease clearly adds to the distortion of epidemiological data available regarding CJD.

In 1994, I began a concerted effort to make CJD a reportable disease. I first contacted the CDC but realized that their interests were more inclined to crises management, their interest being to screen CJD case materials only with regard to outbreaks of the disease. Following the 1995 FDA report of possible contamination of the blood supply by 8 professional blood donors with CJD since the early 1980s, I offered to participate with the CDC attempts to screen Hemophiliac necropsy materials for evidence of the disease. No one ever returned my calls. I continued my efforts to make CJD a reportable disease through the Council of State and Territorial Epidemiologists. My letter proposing this policy was turned down at the annual meeting of the CSTE held in Oregon, May, 1996. I was subsequently told by the CDC that they were only interested in review of pathological CJD materials for evidence of the new British variant of the disease. The CDC recently set up such a screening protocol with the American Association of Neuropathologists and although I offered my services gratis, they decided to stay with their Emerging Infections program based in San Francisco Bay area, again leaving all their eggs in one basket.

In 1994 I communicated with CDC and the NIH laboratory of Persistent Viral infections with regard to setting up a clinical center and data base for CJD here in Mobile. I had set up communication as well with a Neuroepidemiologist at University of San Diego who had been involved in epidemiological studies of BSE in England from the start of that epidemic. We set about to submit to the CDC a proposal to do the epidemiological surveys for CJD in an organized and US wide effort rather than limiting studies to the existing four established emerging infections programs in Minnesota, Oregon, Connecticut and the San Francisco Bay Area. The idea was to pattern it after the United Kingdom CJD surveillance unit. The CDC showed no interest in this approach indicating their only interest was crises management.

As a result we have no idea the extent of the disease in this country, much less the distribution of the agent. Although a preclinical test for the agent is essential in establishing the true epidemiology of CJD in the US, much can be gleaned from making still living CJD cases available for clinical trials or other investigative studies. I believe that the CDC is shortsighted in objecting to such a program.

The CDC was also involved in the debacle in the handling of the possible contamination of blood products by CJD infected professional blood donors. The agencies (CDC & FDA) proceeded with massive withdrawals of blood products with the realization that we are still 10 years away from recombinant DNA production of the

blood factors. The current methodology of filtration of blood products is likely inadequate in controlling contamination by the TSE agent so we are now waiting for the axe to fall again.

ACTIONS OF THE USDA

It is my perception that the USDA are the only agency that has taken the proper initiatives to deal with the problem.

The USDA have held several symposia and national meetings to deal with the problem. They also have invited participation of the British who have dealt with the problem since 1986. APHIS has appeared to be very responsible in surveillance efforts to verify that the US is free of BSE. I have been impressed by the candid remarks made in their handling of potential problems, particularly their investigations of downer cows. The agency has cooperated with industry in dealing with the reliability of rendering processes and it is particularly encouraging that they have placed the science on the table, inviting a look into alternate theories. The recent discrediting of the prion theory by the French researchers seems to show the wisdom of the USDA approach.

The actions of the USDA appears to rely on the success of efforts in the United Kingdom to control the disease. Certain measures such as the June 1988 action to make the disease reportable in the UK, the July 1988 ban on feeding ruminant derived protein supplements to other ruminants, the August 1988 order to slaughter and incinerate BSE suspect cattle, the November 1989 ban to exclude specified beef offal for human consumption, and the September 1990 ban on use of specified bovine offal in any animal feed has resulted in an apparent significant decrease in BSE in the UK with a presumed decrease in danger to humans.

RECOMMENDATIONS:

I suggest to you that we not dwell with these actions in retrospect, especially since we are now enlightened by evidence indicating that the dogma was wrong. Lets go forward. I would like to make the following recommendations.

1) In regard to funding of research efforts; In search for the agent, we should pursue all clues available. The methodology available today for searching out hidden viruses and bacteria in TSE tissues is extremely sensitive and specific. Even more important, these scientific tools are cheap and would require grants in the thousands of dollars rather than millions. It is essential that new monies should not all be given to one or two laboratories, but should be spread out among several laboratories in order to give some fresh approaches. The primary aim of the research should be to develop a preclinical test. In addition we should regroup and study the basic model of the disease wherein the problems currently confronting the FDA and industry indicate that

our basic knowledge of the disease is grossly inadequate. I believe the immune system is very important in the pathogenesis of TSE and should be investigated in a model system. Probably the best model to pursue is in the Squirrel Monkey which is exquisitely susceptible to experimental CJD.

Levels of funding must be increased to encourage other researchers to enter the field. The problem will be solved if we encourage participation of scientists from multiple disciplines, but the rarity of the disease and lack of funding has been an obstacle in getting their attention. PhDs, your true scientists, cannot consider applying for funding without a reasonable probability of getting it. The NIH practice of sequestoring funds directed to TSE research in one or two laboratories has been counter-productive.

2) In regard to epidemiological studies; We must stay away from the crises management approach exhibited by some of the Federal agencies and try to get a handle on the cause of CJD. I believe that CJD and the other TSEs should be reportable so that researchers can have these patients available to test new potential diagnostic tests or therapeutic measures. Perhaps more detailed observations of these patients by expert observors will turn up additional clues. Along those lines, I attempted to set up a clinical center and data base for CJD patients in 1994 which would incorporate educational objectives. Much of the problem with the public perception of the problem is due to lack of understanding of the disease. The inundation of the press with heretical concepts suggesting the agent is uncontrollable has further complicated the situation. The medical profession itself is afraid to deal with the unknown agent, and many physicians and hospitals are unwilling to admit and treat patients or perform autopsies on potential CJD cases. One approach, similar to my efforts in 1994, is to develop a national clinical center for these patients. Perhaps the NIH laboratory of Persistent Viral infections could be the basis for such a program but that agency clearly needs new dynamic and responsible leadership before instituting such a program.

CONCLUSION:

My request to you is that you pursue with haste some new directives for increasing research funds for TSE with emphasis on wider distribution of the resources with less bias. There is at least a dangerous theoretical threat of a future increase in incidence of CJD in this country from the potential contamination of our blood supply and foods, particularly beef products. I do favor a ban on ruminant to ruminant feeding since the practice of feeding cattle their own kind in England likely led to increase in virulence of the agent by adaptation or mutation which resulted in crossing into the human population. Why take the chance of continuing current practices, even if the arguments are that the rendering process is much different here than in England. It is encouraging that control measures instituted in the UK appear to have produced a positive effect. I thank you for your interest.

Mr. SHAYS. Thank you.

Congressman Pappas.

Mr. PAPPAS. Thank you, Mr. Chairman. Gentlemen, thank you for being here and participating. You may have been here in the room during the questioning of the first panel, and one of the lines of questioning that I participated in was in the area of coordination of the research that is ongoing by various Federal agencies and maybe some others.

I am wondering if you both could comment about that. Dr. Hueston, you mentioned that you feel that there is a high degree of coordination and collaboration, and Dr. Bastian, I don't recall seeing what your comment was with regard to that, and if you think that there is a need for a lead agency.

Dr. BASTIAN. I believe there is no question that there is need for a lead agency, and personally, I believe that the NIH should take the ball on this, in taking on the research. Unfortunately, the problem has been that the research has been going down a road of no return, in a sense, and we have to have the research directed in a more unbiased fashion.

Mr. PAPPAS. If I can interrupt, why do you think the NIH should be the lead agency versus another? I am not saying I disagree, I just——

Dr. BASTIAN. Let me say that in my experience so far, probably the most reasonable approach has been so far from the USDA. The USDA, and it seems like I am confusing the issue here, but the USDA has essentially tried to put the science on the table, and through a series of symposia, they, indeed, with inviting both sides of the coin, they have tried to do that. However, the USDA right now is not very well-funded.

The NIH, I believe, needs new direction. I think they have to turn 180 degrees to deal with the problem. But they have the money. My personal feeling is that there has to be a move to take on certain aspects also of the epidemiology. I believe the CDC has not really been interested in CJD until March 20, and as a result, their efforts are, I don't believe, are going in the right direction either. So what you need is a single agency to assume responsibility for the epidemiology, the research, and then this would indeed aid the other agencies in dealing with the problem.

For example, the FDA, they don't have a preclinical test. It's impossible to really be able to make wise decisions without a preclinical test. You've got to do the science. My point is that although we can set up all these regulations, we have to get on the ball and go after the science, and that's why I suggested the NIH because that's been their prerogative up until now.

Mr. PAPPAS. Thank you, Dr. Bastian.

Dr. Hueston, would you answer the same question?

Mr. HUESTON. Yes, sir, the first question being should there be coordination, correct?

Mr. PAPPAS. Yes, and should there be a lead agency.

Mr. HUESTON. I would argue, no, there shouldn't be a lead agency. My experience in the United Kingdom in watching what happened over there is when they attempted to identify a lead agency, that lead agency takes the direction of their major focus. So if you identify a human health agency, they focus on the human health

issues. You identify an animal health agency, they focus on the animal health issues and that is their expertise.

What we have is an excellent opportunity to take advantage of the relative merits and the expertise of different agencies as they apply to a complex problem such as this.

Mr. PAPPAS. And my second question for you both is how effectively do you gentlemen believe that this proposed rule would protect livestock and the citizens of our country for protection from TSEs. I am having to get used to another group of acronyms. When I was involved in county government, human services, they had oodles of acronyms and I used to carry a little card in my pocket. I guess I am going to have to get another card. Go ahead.

Mr. HUESTON. I think it will depend entirely on the degree of compliance, the degree to which they are accepted and implemented, and that brings me back to the proposed rule needs to be understood, needs to be accepted, and the ideal situation would be it comes out of a consensus of all of the effected parties, from the consumer to the producer to the industries associated and the government agencies.

Dr. BASTIAN. I really, can't really deal with that question because I, I would say that the problem in England really resulted from an adaptation or a mutation of the agent from cattle feeding cattle, and surely it does increase the virulence of the breaking of the species barrier and then into humans. But as far as the value or the efficiency of handling the situation in this country by putting these measures in without pursuing the science, I just can't answer that.

Mr. PAPPAS. Thank you, Mr. Chairman.

Mr. SHAYS. Thank you, gentlemen. I am getting a sense of some differences between the two of you. Where would you define the biggest disagreement that you would have, Dr. Hueston, with what Dr. Bastian has said and vice versa.

Mr. HUESTON. I believe what you are seeing is the beauty of science in action, that each of us is taking this from a different perspective.

Mr. SHAYS. Right, but tell me the perspective and why you disagree.

Mr. HUESTON. Dr. Bastian has been addressing the basic issues and basic science questions of the nature of the agent and the development of the disease. I am at the other end of that spectrum in that my field is very applied. Given the information that we have now, what are the realistic measures we can put into place to control the disease. So I come from the standpoint of saying there is an awful lot of science available. There are a number of units around the world working on this disease and more science becomes available on a weekly basis.

So our challenge is to put that information together with some mechanisms and tools to try to come up with an effective and justifiable approach to control the disease. Now, having said that, I think there is a big difference here, that, in other words, I think we can control the disease without a preclinical test.

Mr. SHAYS. Without what?

Mr. HUESTON. Without a preclinical test. A preclinical test would be ideal, but we cannot postpone taking public health and animal health measures until we have a preclinical test. Similarly, it

would be ideal to be able to completely characterize the agent responsible for these diseases. However, we know sufficient information about the agent, I believe, to put into place effective management strategies.

Mr. SHAYS. Dr. Bastian, how would you define the differences? Even if you agree, I would like you to put it in your own words.

Dr. BASTIAN. Well, I think it's a mistake to consider that this is an English problem.

Mr. SHAYS. This is a what problem?

Dr. BASTIAN. I said I think it's a mistake for the agencies or the industry to consider that this is an English problem or a UK problem.

Mr. SHAYS. Right.

Dr. BASTIAN. Because a virulent form of the agent has been unleashed. It clearly—there are patients dying in England from this virulent form of the Creutzfeldt agent. I know Dr. Gibbs tried to say there was no hookup between the agent, the TSE agent and the clinical cases over there. I think that's clearly wrong.

There are two very important papers that show that the pathology in the Macaque monkeys is identical following BSE inoculation to that as seen in the new clinical cases of CJD. And two, Collinge, who studied the changes in the PrP associated with the different infections in England, has clearly shown a signature of the BSE agent that's present in the new cases of the CJD cases.

Mr. SHAYS. I have to tell you, and it's not your fault, but you are losing me a little bit here. I would like to, in more simple terms, just understand the differences between the two of you, and then you want to elaborate. But the purpose is just to help me get a framework for pursuing some other questions.

Dr. BASTIAN. Basically, I agree with Dr. Hueston that some measures have to be taken, and I have no problem with that. But I—my only point is that we have to not—we have to pursue and try to get this preclinical test, or look at an experimental model of the disease in detail to look at the basics of that. If we just put all our efforts into control measures, we may be missing the boat because we just don't have enough information.

Mr. SHAYS. OK. What I think I hear you saying is you need to see a little more proof before you see action taken.

Dr. BASTIAN. No, I am not disagreeing with Dr. Hueston. I realize measures have to be taken in light of what data is available. I don't disagree with that, and I don't disagree with his view of taking these measures at this time. Not at all. My point is that this should not be the only thing we do.

Mr. SHAYS. OK. Well, I think we probably all agree.

Let me just understand. Your basic view is that, and I will quote you in conclusion, "I do not favor a ban on ruminant-to-ruminant feeding since the practice of feeding cattle their own kind in England—"

Dr. BASTIAN. Oh, I do favor.

Mr. SHAYS. You do favor.

Dr. BASTIAN. Yes.

Mr. SHAYS. You do favor a ban on ruminant-to-ruminant feeding, in spite of the fact that we don't have a definitive sense.

Dr. BASTIAN. Correct.

Mr. SHAYS. Why would you favor that?

Dr. BASTIAN. Again, I believe we have to act. We have to set up some regulations. My point is in regard to getting more definitive tests so that we can—in a sense, for example, in a sense possibly have enough data down the road to be able to remove such bans.

Mr. SHAYS. It's conceivable that this whole effort, banning ruminant-to-ruminant feeding, is not the problem. You are shaking your head.

Dr. BASTIAN. I don't see that—I am sorry.

Mr. SHAYS. No, I was looking at Dr. Hueston. You were shaking your head so I would like to translate that.

Mr. HUESTON. Right, I believe there is overwhelming evidence to suggest that it was the recycling of feeding of ruminant-derived protein that led to the epidemic in the animals——

Mr. SHAYS. And that involves the prions.

Mr. HUESTON. Well, in my hypothesis, it could be the prions, it could be another agent.

Mr. SHAYS. OK. The feeding process of ruminant-to-ruminant, there is consensus, then the question is what is the cause with that process of feeding—the prion bacteria, correct?

Mr. HUESTON. Right, the discussion of what is the agent, the actual ideological agent within that material.

Mr. SHAYS. So there is agreement on the process of transfer. We just don't know what the agent is.

Mr. HUESTON. Correct.

Dr. BASTIAN. We've essentially, by this mechanism, created a pattern of serial passage, and serial passage where you would inoculate a bacterium into an animal and take it from one animal to another, you can clearly increase the virulence of the organism, and I believe that's exactly what's happened in the English experience.

Mr. SHAYS. It's, in sense, a compounding.

Dr. BASTIAN. It's a classic experiment with bacteria. You can increase the virulence of the organism by simply serial passage in an animal model.

Mr. SHAYS. Dr. Hueston, what if Dr. Bastian is right?

Mr. HUESTON. What if he is right in terms of the spiroplasma?

Mr. SHAYS. Yes, when will it start to matter?

Mr. HUESTON. If we look at this recycling or process of incorporating animal-derived proteins into animal feeds, it involves a process called rendering and that involves heating and treatment of the material, and that heating and treatment of the material destroyed, we felt up until 10 years ago, destroyed all of the potential agents that might cause disease and it was an ecologically sound method of recycling a waste product, if you will, into a usable form.

Now, it even—in fact, the processes that are being discussed and the processes that could be provided can inactivate some of the agents like the one Dr. Bastian is discussing. I think as we first take the control measures that are prudent, upon which we can get a large degree of compliance, and then as more information becomes available, we modify, adjust, update those recommendations to take advantage of the new information.

Mr. SHAYS. One of the things that was clear to me when Dr. Gibbs spoke, and you as well, Dr. Bastian, both of you have been

in this field a long period of time and you are expert witnesses. I wasn't sure we needed you to do that except for the fact that I get the sense that I could probably count on my hands or hands and toes the number of people who are in this field in the United States. Is this a really small group?

Dr. BASTIAN. That is the problem. And one major problem has been that you have not been able to attract what I consider the true scientists, the Ph.D.'s that are slaving in the university settings. There is no money available, and so you've got to be able to attract these people.

Mr. SHAYS. This is not meant to be a digression, but in these hearings we have on the Gulf war illnesses syndrome, you know, many potential causes and many effects from those causes, we have found that there seem to be very few people who have gotten into the whole issue of detecting chemical exposure and knowing how to treat it, and we're being told that—and it's been really a surprise to me that there aren't more in the FDA, or excuse me, the VA or DOD or Pentagon who have this expertise. And I have to believe in the market process, but sometimes there becomes a disincentive to get in these fields, and I particularly feel in terms of chemical exposure and detection and treatment, that we need many more people in that field.

So what would guide us, then, because you obviously, Dr. Bastian, are sensitive to the fact that institutes of health are one primary way of responding to the lack of market focus, and so I sense from you you are a little unhappy with the institutes of health and how they have allocated funds in this area.

Dr. BASTIAN. The problem has been that all of the research has gone in one direction, that's correct, and basically the prion theory, for example, it just expands to incorporate new data. It doesn't matter how much—I mentioned putting more money into the field, it doesn't matter how much more money you put into the field if the research is not going in the right direction. My point being that we've got to consider all the clues out there.

There is one fascinating study that was published in May wherein a group in New York inoculated hay mites into mice and produced scrapie. Now, these—this was based on the fact that in England at a very early time that fields that had scrapie-infected animals, if they removed the animals and put fresh animals in, the new animals came down with the disease.

So they took the hay mites in those fields and inoculated them and produced the disease. So there was something in the hay mites that produced scrapie. They then took the mite preparation, did immunological cross-reactivity studies with the scrapie antibodies and indeed showed cross-reactivity. So there was something reacting in the hay mites to the scrapie antibody. However, they have not been able to find the PrP gene, and I suspect that there is a spiroplasma in those hay mites.

Mr. SHAYS. The prion.

Dr. BASTIAN. Yes, the prion, they have not been able to find the prion gene. So what they are likely showing by immunological cross-reactivity is antibodies developed to the scrapie from—how you prepare the antibodies in scrapie is take the scrapie material,

inoculate into rabbits, and the rabbit produces antibodies to these proteins that are inoculated.

Now, what I suspect is that the—what's been produced in those, the scrapie antibodies, is an antibody to the agent, which I believe is the spiroplasma, and I am sure that's what's reacting in those hay mites is likely to be a spiroplasma. What's fascinating is I was told by personal communication that hay mites that are not infectious, that is those that do not produce the disease, also show immunological cross-reactivity with the scrapie proteins, and in that sense——

Mr. SHAYS. So what's the bottom line to your point though?

Dr. BASTIAN. My point is that this is further evidence, the prion not being the answer.

Mr. SHAYS. OK.

Dr. BASTIAN. And if you are going to put money into, if you are going to solve this problem, you are going to have to check all possibilities.

Mr. HUESTON. Congressman Shays, may I try to put some of this research into perspective?

Mr. SHAYS. I am going to conclude fairly soon. I am going to invite Dr. Gibbs and Dr. Detwiler to come back afterwards to make a short comment or observation, if you like. You don't have to, but my philosophy is if people are willing to stay through the hearing and hear other comments, would like further input. So we appreciate that both of you stayed.

Dr. Hueston.

Mr. HUESTON. Thank you. Prior to the identification of bovine spongiform encephalopathy, the majority of the published research about these transmissible spongiform encephalopathies actually originated in the United States, and certainly that was readily the case with the human forms of the disease and much of it came out of the NIH lab. We have currently in the United States a number of groups evaluating the human spongiform encephalopathies, looking at animal diseases such as chronic wasting disease, looking at the scrapie and groups that study transmissible mink encephalopathy. So there are groups and there is activity continuing in the United States.

I think that Dr. Bastian is making a very important point to say that we should always maintain a healthy skepticism to make sure that we aren't tracking down the wrong path, and that there is a need to encourage other approaches and other examinations of this issue. As it might relate, just for your information——

Mr. SHAYS. I think he was saying a little more. I think he was saying there is research that would suggest that, so I think he was saying more than healthful.

Dr. BASTIAN. Right.

Mr. HUESTON. Recall there are people around the world who continue to put forth a whole range of theories for the origin, for the etiological agent associated with these.

Mr. SHAYS. Right, but one of the questions would be, and I am sorry to interrupt, is: are we putting too much in one area, or are we putting enough there, but should we put more in another area? That's one of the points I am hearing and you probably wouldn't disagree with that.

Mr. HUESTON. I wouldn't disagree.

Mr. SHAYS. I am sorry. Continue.

Mr. HUESTON. I just want to make one other point. Essentially all, the vast majority or essentially all the work right now on bovine spongiform encephalopathy is happening overseas. And we are quite comfortable, in fact, encouraging that that be the case because we don't want the agent coming into the United States even for experimental work in laboratories. So that's another reinforcement of why the collaboration is extremely important, so that we can work with our collaborators in other countries where they experience disease to preclude as one more further protection from that agent coming into the United States.

Mr. SHAYS. Is there any question you wish I had asked you or the committee had asked you, any point you want to put on the record? If there is, I would be happy for you to put that question on the record yourselves.

Mr. HUESTON. I will address one. I think it is very easy—increasingly, I've been studying the animal health policy. How would you implement policy and what is the most effective means for controlling and preventing disease with policies, and there is some interesting recognitions. One is the question of reportable diseases. One thing that Dr. Bastian suggested or put forth is his opinion that Creutzfeldt-Jakob should become a reportable disease.

From my experience with animals' diseases and watching the British situation, from the moment one makes a disease reportable, the actual reporting of the disease decreases. So we have an interesting human phenomenon going on here. As an example, in Great Britain, when they were recently mandated by the European Community to make scrapie reportable, the reported cases of scrapie in sheep in Great Britain dropped over half. I do not believe that that is because of the miraculous beneficial effects of making a disease reportable.

Mr. SHAYS. I could make my observation that they wanted reportable because they were going to take some fairly drastic action, and Dr. Bastian, I don't mean to put words in your mouth, but I wonder if that analogy would be appropriate. In other words, that if we did it, it would have that same effect.

Mr. HUESTON. Well, in the discussions to make Creutzfeldt-Jakob reportable in the United Kingdom, it is the consensus of the public health authorities that making the disease reportable would reduce the reporting and the likelihood of followup on the cases.

Mr. SHAYS. If that is true then we should not have any reportable diseases.

Mr. HUESTON. I think it depends a lot on the specific diseases. May I take you for a second, having talked to families, I don't know if you've had the opportunity to work with families as Dr. Bastian and I have visited with families that have cases of CJD. This is a very, relatively rapid onset, it's a degenerative disease that's ultimately fatal. There are a lot of questions the families have that can't be answered and it leads to a tremendous amount of emotion, grief, and concern, and families are understandably extremely apprehensive about being identified with a——

Mr. SHAYS. One second here. We're getting an echo. I think it's one of the mikes. Take your time.

Thank you for doing that.

Mr. HUESTON. So the challenge is that if the disease is made reportable and my concern was, as you can imagine, there is a great deal of attention on the families where this disease is reported. The families lose a lot of their privacy, so the feeling is if the disease was made reportable, they would have less chance to trace back to the families and ask the important questions that we need to further understand the disease.

Dr. BASTIAN. As a physician, I disagree with Dr. Hueston on that, because the families are desperate for information. The families are willing to participate in any sort of effort. In fact, I've received several calls this past week from families that asked what can we do, how can we help resolve some of the information regarding this. And my—a major problem in this whole field is the fear that's been placed amongst the medical profession about this. People are afraid to handle the patient.

I received a call from a physician, a neurologist in Florida, and he said I have a patient I believe has Creutzfeldt-Jakob disease. The hospital will not admit the patient. If I got the patient admitted, the neurosurgeon would not biopsy it, and the pathologist will never autopsy the case. How on earth are you going to make a diagnosis?

Now, this clinical test that Dr. Gibbs put forth, my personal experience with that, it was based on a, on the finding of abnormal proteins in the spinal fluid. It's got nothing to do with PrP, but there are abnormal proteins occurring in the spinal fluid in a significant number of these patients. But it's also seen in other diseases, like herpes encephalitis and recent stroke.

So in the right clinical setting, the test is maybe useful, but in a personal experience, I received a brain biopsy from a patient submitted to me from Tampa, FL, by the neuropathologist, and I looked the biopsy and saw spongiform encephalopathy, Creutzfeldt-Jakob disease. And he said well, we sent some—the spinal fluid test is negative. I said I don't care, this is Creutzfeldt-Jake disease.

The patient died about a year later and I received the brain for examination and clearly had Creutzfeldt-Jakob disease. But the neuropathologist said, you know, we sent four specimens of CSF over this time period, for examination of CSF for this unusual protein, and we finally got a positive. This test could be very important, except that from the recent data, it appears not to be positive until the disease has occurred or is about to appear. And my point is that before we offer this as a solution, let's test this in an adequate model system, and right now there has not been a good model system for this disease.

For example, with the poor FDA people dealing with the blood products, they don't—one, we don't know if the blood is infectious. Two, we don't know if it is infectious, we don't know at what phase of the disease it is infectious. We have no basic information. The point is in making all these decisions and control measures, which I think have to be done, I am not saying don't do it.

Mr. SHAYS. I understand.

Dr. BASTIAN. But you've got to go ahead and try to get some of the basic information to try to make a common sense decision on some of this. And we don't have that as yet.

Mr. SHAYS. OK. I think I am fairly clear and the committee is fairly clear on that. Is there any other comment you want to make?

Dr. Gibbs, I'd be happy to have you come up and make a comment if you like. We're not going to resolve all the world's problems today, but we're just trying to get a focus for the committee.

Dr. GIBBS. Thank God we don't have to solve the world's problems. First of all, let me just say if there is anything we have learned from the outbreak of BSE in the United Kingdom, we should have learned it very strongly, and that is stop feeding ruminant to ruminant. I think the evidence is clear in that regard.

Mr. SHAYS. And let me just say, I am going to interrupt you to say when we had our previous hearing, there was consensus among a large number who testified except those who were involved in the feeding process themselves, who wanted very much for the FDA to take that action and we asked each one specifically. So there was consensus at our hearing certainly that the FDA do exactly what they have done.

Mr. GIBBS. The second point I would like to make was with regard to some of Dr. Bastian's comments, and that is you may have missed it in my testimony. Certainly, I will submit it to the written testimony, and that is my laboratory is not the only laboratory at the NIH working on these diseases. You have the Rocky Mountain Laboratory in Hamilton, MT, part of the Allergy and Infectious Disease Institute working on it.

The most important thing to remember is my budget is an intramural budget, far below the many millions of dollars that are given in extramural programs by grants to academia and so forth. Our grant program undergoes peer review and is rated on peer review, not by NIH personnel, but by people from academia, and if you receive a high enough score on your proposal, you are approved. If your score is really good, you are funded.

Mr. SHAYS. Let me ask you, isn't there always the potential, obviously there is always potential, but more than potential here, particularly with orphan diseases, which this is, in fact, an orphan disease, correct, in the sense that there is not many have it, and therefore the private factor is not going to be out there funding out of market reasons. Isn't there always the concern that you just don't have enough of your like-minded people on those peer reviews to consider it, you know, your application?

Mr. GIBBS. That's a possibility, but in this regard, I think this field is what I put on the frontier of medicine, and is so important, that I don't think you would find that problem. I think if it is good research, it's going to be funded. And I don't think there is a feeling of competitiveness in the sense of, well, we won't fund this because he's in this institution.

Mr. SHAYS. I don't think it's as obvious, but one of the things this committee may do, is in fact,—we may not do it, but we may look at the whole issue of how studies are done, research is done, and who decides. Because we hear a number of people complain. Obviously, they tend to be people who didn't get necessarily their project funded and so on, and then there are people who seem to be automatically in the system repeated without even having to make applications, and it continues, and you just wonder if they are no longer there if that project wouldn't stop and then go.

Mr. GIBBS. Well, certainly there is a point to be considered here, and that is as you pointed out earlier, there are relatively few laboratories in the United States working on these diseases, that's No. 1. And No. 2, those that are working on this disease, by and large, form a community, and as I see it, a fair number of those, outside of government, are well supported by not only NIH grants, but by USDA grants, FDA grants, and by the private sector, foundations.

Mr. SHAYS. Dr. Bastian—thank you, Dr. Gibbs, I appreciate it.

Mr. GIBBS. I had one other thing, please. In regard to Dr. Bastian's comments about the tests that I submitted here, and that is you will see that it has a 99 percent sensitivity and a 99 percent specificity. Now, there is no problem clinically diagnosing herpes encephalopathy from Creutzfeldt-Jakob disease. But we recognize the test does pick up herpes encephalopathy.

Mr. SHAYS. Right.

Mr. GIBBS. But clinically you can separate those two, and our test is also beneficial in testing the spinal fluid of cattle experimentally infected with scrapie and mink encephalopathy and sheep with naturally occurring scrapie.

Mr. SHAYS. Dr. Hueston, any other comment you would like to make?

Mr. HUESTON. No, sir, thank you.

Mr. SHAYS. Thank you.

Dr. BASTIAN. I think regarding the test, the question is is the test positive in a certain period of the disease? It may be extremely important, but we just don't know, from my experience, my personal experience, we just don't know how this will fit into the picture. And so in an animal model, you could test that.

Mr. GIBBS. Those studies are underway right now.

Mr. SHAYS. Let me just say to you, the last thing I want to do is get into the specifics of a particular study, but Dr. Gibbs, I think what I am hearing Dr. Bastian say is that, you know, we're going down one trail and he would argue, it seems to me, that we're going, you know, with a lot more energy down that trail and we also should be going down this other trail. And I think I am hearing him say that we're not doing that to the extent we should. And, you know, that's a judgment call. I mean, he's telling the committee that's his opinion, and it's something we would—what I am saying is I don't care to resolve that issue today.

Mr. GIBBS. OK.

Mr. SHAYS. OK. Is that all right? I have a lot of respect for both of you and all the others who have come and it's been very helpful and we'll try to sort out of the some stuff.

Mr. GIBBS. If we can be of further assistance, we are standing by.

Mr. SHAYS. I was thinking of the staff member, and Mary, where does she get all these good panelists. She did it again.

Mr. GIBBS. Well, I live on the Hill, I don't necessarily like to travel to the Hill.

Mr. SHAYS. Thank you. This hearing is adjourned.

[Whereupon, at 4:10 p.m., the subcommittee was adjourned.]

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